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MARIHUANA AND HEALTH

FIFTH ANNUAL REPORT

TO THE

U.S. CONGRESS

FROM THE

SECRETARY OF HEALTH, EDUCATION, AND WELFARE, 1975

PREPARED FOR THE

SUBCOMMITTEE ON ALCOHOLISM AND NARCOTICS

OF THE

COMMITTEE ON LABOR AND PUBLIC WELFARE
UNITED STATES SENATE

AUGUST 1976

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FOREWORD

The ongoing debate over marihuana has always been among the most schizophrenic of our national drug abuse policy issues.

On the one hand, we are struggling toward an understanding of the complex dysfunctional effects of heroin on our society, and attempting vigorously to develop programs to reduce both the supply and demand of this, as well as other dangerous illicit drugs.

In addition, we are taking a cold, hard look at many of our prescription and over-the-counter drugs, asking whether there needs to be further restrictions or more rigorous controls over many of them, due to the adverse health consequences they may well entail.

We are looking with disfavor, for example, upon our increasing reliance on tranquilizers and other anti-depressant drugs. We are viewing with alarm the hawking of over-the-counter remedies during popular, child-oriented television programs, commercials which teach our children that one drug is better than another for a headache—but not (as psychiatrist Gerald Shulman pointed out in recent hearings) that a headache is a perfectly natural way for the human body to express its own momentary need for relaxation and quiet, and that dulling the pain could sometimes be the worst possible solution to that type of medical problem.

We are worried, in short, about becoming a chemical culture, a nation of people whose solution to every little problem is a drink or a pill.

Only with regard to marihuana, on the other hand, do "liberal" minds appear to be moving in the opposite direction.

Many States are considering the decriminalization of the possession of marihuana, and some have already enacted such laws.

For the first time, national survey data indicate that a majority of persons in the 18 to 25 age bracket have tried marihuana. Thus, even if the drug is to become completely legal, as is alcohol or tobacco, it would be even more important for us to understand as many of its potential health consequences as is possible. For it is important to bear in mind that, while heavy penalties for possession or use do not themselves create (or even necessarily reflect) sinister medical dangers from a substance, neither does legalization or decriminalization magically remove any such dangers, if they actually exist.

It is imperative, then, regardless of our opinion about decriminalization, that we continue our inquiry into the health consequences of marihuana use and abuse. This Fifth Annual Report makes many valuable contributions to that inquiry.

HARRISON A. WILLIAMS, JR.,
Chairman.

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LETTER OF TRANSMITTAL

U.S. SENATE,
COMMITTEE ON LABOR AND PUBLIC WELFARE,
Washington, D.C., July 21, 1976.

Hon. HARRISON A. WILLIAMS, Jr.,
Chairman, Committee on Labor and Public Welfare, Dirksen Senate Office Building, Washington, D.C.

DEAR MR. CHAIRMAN: I am pleased to transmit to you the fifth annual report by the Secretary of Health, Education, and Welfare on Marihuana and Health. The annual publication of this report is required by Title V of Public Law 91–296. It contains the latest scientific findings on the health consequences of marihuana use. This report has proven to be a valuable educational tool and policy guide to inform the public on the issues surrounding the effects of using (and abusing) marihuana.

I am pleased, therefore, to transmit *Marihuana and Health, Fifth Annual Report to the U.S. Congress from the Secretary of Health, Education, and Welfare* to you and to recommend its distribution by the Committee.

Sincerely,

WILLIAM D. HATHAWAY,
Chairman, Subcommittee on Alcoholism & Narcotics.

ACKNOWLEDGMENTS

As has been true in the past, preparation of the fifth annual *Marihuana and Health* Report was made easier by the generous cooperation of the many members of the scientific community who supplied useful information on their current marihuana research. Their contribution is gratefully acknowledged.

The technical chapters were written by knowledgeable members of the research community who generously gave of their time on short notice to maintain a tight production schedule. They are:

Dr. Sidney Cohen, University of California at Los Angeles, Chapter 9, Therapeutic Aspects;

Dr. Douglas Ferraro, University of New Mexico, Albuquerque, Chapters 4, 5 and 6, dealing with preclinical unlearned and learned behavior and with chronic effects on both;

Drs. Lissy Jarvik and Steven Matsuyama, University of California at Los Angeles, Chapter 8, Effects on the Genetic and Immune Systems;

Dr. Reese Jones, Langley-Porter Neuropsychiatric Institute, San Francisco, Chapter 7, Human Effects;

Dr. Ralph Karler, University of Utah, Chapters 2 and 3, dealing with Chemistry and Metabolism and with Toxicological and Pharmacological Effects; and

Dr. William McGlothlin, University of California at Los Angeles, Chapter 1, Epidemiology of Marihuana Use.

Scientists on the staff of the National Institute on Drug Abuse who contributed to the report in a variety of ways include: Drs. Monique Braude, Norman Krasnegor, Daniel Lettieri, William Pollin, Joan Rittenhouse, Louise Richards, Stephen Szara, Robert Willette and Ms. Eleanor Carroll.

Thanks are also due to Ms. Georgette Semick, Carol Tuckerman and Dr. Michael Rumsey for their editorial and production skills.

Dr. Robert C. Petersen wrote the summary of the Report and as senior editor had primary responsibility for its overall preparation.

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INTRODUCTION

Marihuana, an issue once marked by emotionalism, is increasingly being examined thoughtfully. Much has been learned about marihuana use and its personal and social consequences. Yet, much remains to be understood. It is clear that marihuana is not a subject for simplistic analysis.

This present edition of "Marihuana and Health" represents the fifth in a series of annual reports from the Secretary of Health, Education, and Welfare to the Congress as required by Title V of Public Law 91–296. Last year, the fourth report in this series raised fundamental questions about the role of cannabis in altering the body's immune response, endocrine functioning and basic cell metabolism. Although more data are now available, the direct health implications of these earlier laboratory findings are still not certain.

There is little question that marihuana intoxication, like alcohol intoxication, poses significant hazards. For example, psychomotor performance is impaired by cannabis intoxication. This can have dangerous consequences in such areas as traffic safety and industrial performance. Intellectual performance and in particular, immediate memory, are also impaired while under the influence of the drug. Since marihuana is the third most widely used recreational drug—exceeded only by alcohol and tobacco—any adverse implications of its use are likely to be far-reaching.

It has become increasingly clear that marihuana use is inextricably bound up with the use of many other drugs. Those who use other licit and illicit drugs are far more likely to use marihuana than those who do not. Conversely, heavy marihuana users are more likely than those who are not, to use other drugs as well. While it was once thought, for example, that marihuana users were less likely to use alcohol than nonusers, it is now evident that they are, in fact, more likely to do so. Frequently the two drugs are used simultaneously—a combination that may be more hazardous than either used alone.

The increasing availability of higher potency materials makes it more likely that adverse consequences will ensue if the use of these stronger cannabis preparations becomes widespread.

This report does not give marihuana a "clean bill of health," as some would hope. Nor does it support the fear and irrationality that still characterize some of the public debate about marihuana. Instead, it is a progress report on our effort to understand a challenging health problem with immense social, political, and economic implications.

This year, in order to provide a somewhat broader perspective, the report is being issued as a general overview accompanied by a series of technical chapters which discuss the research findings in greater detail. In this manner we hope to better serve the needs of both the general reader and the research specialists.

Robert L. DuPont, M.D.,
Director, National Institute on Drug Abuse.

SUMMARY

Marihuana and Health, 1975: Summary and Overview

EXTENT AND NATURE OF USE

Present evidence indicates that cannabis use has significantly increased among Americans during the last two years.

Throughout most of its history American marihuana use has consistently involved a minority of any national age group; however, the most recent national survey data indicate that in the 18–25 age group a majority (53%) have now tried the drug, up from 48% in 1972. Among those surveyed under 18, nearly one in four (23%) has ever tried marihuana—an increase from the one in seven (14%) who reported in the 1972 survey ever having done so.

Current use—defined as use within the past month preceding the survey—has also significantly increased among those under 18. Seven percent reported such use in 1972, 12% did so in the most recent survey. There does not appear to have been a similar increase in such use among those over 18—among whom current use has remained the same or has slightly diminished depending on age, since 1972.

When questioned regarding their plans for future use, one third of those who have used marihuana indicate they definitely intend to do so again. Another third of this group indicate they might do so. Slightly smaller numbers of adults than of youths indicated their intention to continue use (1–1).

While there has been an increase in use by high school and junior high school age groups (attested to by both local and national survey results), future trends of marihuana use in America continue to be uncertain. Despite the other increases noted, use among adults has not increased. In part, this may be explained by research reported in the fourth Marihuana and Health report: changes such as marriage, parenthood and the assumption of other adult roles are inimical to continued marihuana use.

Support for the above interpretations is also found in data garnered from research conducted on a national sample of 20–30 year old men. This nationwide survey found that even within this restricted age group, larger proportions of the men in the younger subgroups used marihuana than did those who were older. Men pursuing more conventional life styles in that they were married and employed full time, were considerably less likely to be using marihuana than were either the unmarried or the unemployed (1–23).

Although there is good evidence of a continuing increase in marihuana use among younger people, there is little indication that such

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Note.—Numbers in parentheses refer to the several technical chapters and their lists of references. Thus, 1–1 refers to reference one in Chapter 1. This is the specific study from which the data are abstracted.

use has come to involve a significant proportion of the older population. For example, if we examine the behavior of those ages 26–34, in contrast to the 18–25 age group less than one third (29%) have ever used marihuana compared to over half (53%) of the younger group. One in four of the 18–25 group had, in fact, used in the month preceding the survey but less than one in twelve (8%) of those 26–34 had done so. In still older age groups use is even less common. Only 7% of those between 35–49 have ever used and only 2% of those over 50 have ever done so. Less than one in one hundred of the over 35 group had used during the month prior to the interview (1–1).

Despite the indications that marihuana has not become popular with older groups and the evidence that its use may be diminished as adult roles are adopted, any prediction regarding the future of cannabis in American society must be hedged with caution. A Gallup poll conducted in 1967 among college students indicated that only one in twenty had ever used the substance, but by 1974 over half (55%) reported use in the Gallup survey (1–9). In seven years, what was once clearly statistically deviant behavior has become the norm for this age group. While in previous years use was correlated with level of education, the percentage now reporting marihuana use is virtually identical for high school drop-outs, high school graduates and college graduates in similar age ranges.

National trends and use patterns mask distinctly different patterns in particular communities or geographical areas. In one Northern California county in which a survey of junior and senior high school students has been conducted each year since 1968, even the earliest findings indicated over one quarter of the ninth grade males (27%) had had some experience with marihuana during the previous year. Among male seniors nearly half (45%) reported use in the year preceding. Current (1975) comparable figures are now 49% for ninth graders and 64% for senior boys. However, the percentage reporting use on 50 or more occasions in the previous year has not markedly increased for the past five consecutive years (1971–1975) (1–4).

During the past five years since the first Marihuana and Health report, cannabis use in the United States has changed in character. Originally marihuana's popularity was concentrated among young people associated with a "counter culture." It was regarded as symbolic of their opposition to traditional values and to the prevailing political climate (Cf. the first Report, 1971).

As use has spread to involve larger numbers and to more conservative segments—it has now been experienced by a majority in many groups—it has lost some of its nontraditional, antiestablishment symbolism. Early use often involved opposition to more traditional alcohol use. Now those who use marihuana are also very likely to use alcohol—frequently simultaneously. Marihuana use seems unlikely to displace more traditional alcohol use even among the young. Continuing research on patterns of multiple drug use and drug using contingencies may better enable us to predict both individual and group drug use.

Use patterns in other countries, even those in which cannabis use has been endemic for many years, provide few clues to future use in the United States. In other countries use is typically class related with the lower classes, the traditional users. While in some of these coun-

tries of traditional use there are now middle or upper class users, such users seem to have adopted marihuana as part of an international youth culture rather than by diffusion from native users. Expectations with respect to drug effects also differ in that traditional users do not share the recreational orientation that characterizes American users.

CHEMISTRY AND CHARACTERISTICS OF CANNABIS

Although a detailed discussion of developments in cannabinoid chemistry is of primary interest to the specialist, there is a range of developments of more general interest. The plant, *cannabis sativa*, far from being a simple substance is, in fact, chemically quite complex. The last several years of research have resulted in an increasingly sophisticated knowledge about this complex substance. There is a growing awareness of the need to much more adequately describe several major cannabis constituents if we are to adequately specify the nature of the material. The United Nations has now recommended that all research reports on cannabis describe not only the amount of delta-9-tetrahydrocannabinol (the major psychoactive ingredient) but that of cannabidiol and cannabinol as well.

The ability to synthesize various chemical components of marihuana as well as the drug's metabolites (i.e., compounds resulting from the biological transformation of the originally ingested material) is a significant advance. Availability of such pure substances provides researchers with necessary materials for careful study of the physiological role of marihuana's various components.

While primary interest has tended to center on delta-9-THC because of its role as the principal psychoactive ingredient in cannabis, the part played by several other ingredients may be important in producing other cannabis effects. These other ingredients alone or in combination, may account for possible adverse health consequences or contribute to the possible therapeutic usefulness of the drug.

The detection and analysis of marihuana in body contents such as blood, saliva, urine and breath is a problem important both to basic research and to forensic medical applications. For research, it is important to develop methods that accurately determine how much smoked or otherwise ingested marihuana actually becomes physiologically available. These amounts may be substantially different than the amount ingested because of losses that occur in consuming marihuana, delayed bodily absorption, and individual differences in ability to metabolize the drug.

In the clinical setting, appropriate treatment of the unconscious patient brought to the Emergency Room following an accident may be dependent on knowing whether he or she is marihuana intoxicated. In other medical situations being able to determine with certainty the level or fact of being intoxicated may make the diagnosis of the patient much easier.

The general increase in marihuana use has undoubtedly brought with it an increase in the numbers who drive while cannabis intoxicated. Recent evidence (Cf. Driving Effects) further confirms cannabis adversely affects driving. Thus, there is a real need for the development of one or more roadside methods that can be rapidly employed in much the same way as current tests for alcohol intoxication.

Although simple, rapid detection methods are badly needed, detecting marihuana use is inherently much more difficult than detecting alcohol use. The quantities of drug involved are much smaller and they are very rapidly transformed into metabolites which differ chemically from the originally consumed material. As with alcohol, it is important to quantify the level of use for all of the purposes outlined. During the past year considerable progress has been made in improving detection techniques.

In addition to newer, thin layed chromatography and high pressure liquid chromatography methods, two other techniques have shown unusual promise. Radioimmunoassay (RIA) is a technique in which an antibody specific to a drug or its metabolites is developed and then "tagged" by means of a radioactive molecule in its structure. When a solution of the tagged antibodies and of the body fluid in which the drug to be detected is made, the radioactive markers are displaced proportionately to the drug quantity present. The accuracy of RIA is now being compared with that of more cumbersome procedures.

A second technique under development is called the enzyme multiplied immunoassay test, or EMIT. The antibody reaction which is its basis is similar to that used in the radioimmunoassay technique. EMIT has the added advantages of involving less work, less sophisticated equipment and is more rapid thus making it more suitable for rapid screening. Field trials on EMIT are ongoing.

A third method which also shows promise of shortly becoming available is likely to be most useful for traffic safety purposes. It utilizes breath samples in a manner roughly analogous to present roadside alcohol intoxication detection.

As has been repeatedly emphasized, marihuana and hashish vary widely in THC content and thus in their ability to intoxicate. This variability results from differences in plant genetic origin, conditions of cultivation and preparation of the material including the degree of concentration of leaves and flowering tops. A relatively recent addition to the illicit market is hashish oil, a substance having a THC concentration of 40–50% as compared to the 1–2% THC content of most marihuana ordinarily available in the United States. Increasing availability of such more potent cannabis preparations may have quite different implications from the more commonly used, weaker preparations that have been available in the past. Use of stronger material, particularly by relatively naive users unaccustomed to its effects, is considerably more likely to result in acute panic and other adverse reactions. Stronger cannabis and cannabis derivatives used under conditions in which the dose is more difficult to control, may also result in marked impairment in driving or other complex psychomotor skills. Such unexpected effects could have serious implications.

ANIMAL RESEARCH

A wide range of research on the effects of marihuana has been conducted with animals because their genetic and learning histories, unlike those of humans, can be accurately specified. Animal models also permit the use of high doses and other procedures not possible in human research. Apart from studies of various physiological effects

of the drug which have been discussed primarily in relation to human findings, there are some behavioral observations in animals that are of interest.

Because there has been some question about the role of marihuana as a possible releaser of aggression, studies of animal aggression following marihuana or THC administration have been done. Generally, these drugs have been consistently found to suppress aggression when the animals are not under stress. When animals are stressed by a variety of means (e.g., food deprivation, sleep deprivation, morphine withdrawal, etc.) THC or marihuana tends to increase aggression.

The results of behavioral studies in animals suggest that the effects of cannabis on aggression may be complexly related to the degree to which the animal is subject to stress and the length of time over which it has received the drug. The degree to which these observations are relevant to human behavior is unknown although they do provide a basis for devising related human studies.

In an experiment which studied monkeys in three to six member social groups several changes of interest were found. Given oral doses equivalent to very heavy human cannabis use, the monkeys responded much like humans. They slept and rested more frequently; active social interaction such as grooming of others was reduced. Over more extended periods of administration, the monkeys gradually showed less and less of these effects. While aggression was initially reduced, after receiving THC for weeks or months during the year-long study the monkeys became irritable and aggressive (hitting, biting, chasing behavior increased). There was no evidence of the reduction in testosterone levels that has been reported in humans nor were menstrual cycles of females apparently disturbed (4–67).

More detailed discussion of the extensive research that has been done with animals is to be found in the technical chapters of this report.

HUMAN EFFECTS AND HEALTH IMPLICATIONS

Effects of marihuana can conveniently be divided into: (1) the acute effects of cannabis intoxication and (2) the longer range consequences of regular or chronic use. It is considerably easier to study acute effects and so after eight years of intensive investigations many, if not most, of these effects have been elucidated.

Human acute physiological effects

An increase in heart rate and a reddening of the eyes have been the most consistently reported physiological effects of marihuana. Heart rate increases are closely dose related. Early awareness of this marihuana-induced tachycardia created concern over possible adverse cardiovascular effects of the drug especially in those with coronary disease. Several reports issued in the past year have confirmed a preliminary finding from last year. Marihuana use decreases exercise tolerance prior to the onset of chest pain (angina) in those with heart disease (7–137, 3, 4). Use of those with already existing cardiovascular deficiencies, therefore, appears to be unwise. The contrasting finding that marihuana produces minimal changes in heart function (aside from a rate increase) in young, healthy men illustrates that the drug's effects

may significantly differ in persons with pre-existing medical problems from those in normals.

A number of reports have confirmed and extended initial evidence that smoked marihuana when acutely administered, results in improved pulmonary function as measured by bronchodilation (7–156, 157, 158). Optimism created by this finding has since been tempered by evidence that under conditions of more chronic use pulmonary function is impaired, rather than enhanced (7–62).

Evidence that marihuana and especially its principal psychoactive ingredient, delta-9-THC, are effective in reducing intraocular pressure in both normals and in glaucoma patients has been further confirmed. While some question exists whether this effect is due to a nonspecific drug-induced relaxation shared with other sedative drugs or to a more specific marihuana reaction, more recent evidence suggests it is THC-specific (Cf. Therapeutic Aspects).

Understanding of the metabolism and the mechanisms of action responsible for various marihuana effects has increased although many questions remain open.

More sophisticated attempts to measure various aspects of psychological and psychomotor performance have been generally consonant with subjective reports. Impaired memory, altered time sense and performance decrements on a variety of tasks have been experimentally confirmed. Generally, the more complex the task, the greater the degree of disruption produced by acute intoxication. Tasks which are relatively simple and with which the person is familiar are minimally affected. As the task becomes more demanding and novel and/or the dose of drug increases, performance decrements become larger. At lower doses, evidence confirms users' assertions that they are often able to "suppress the marihuana high" when the situations so demand.

Although users have reported enhanced auditory, visual and tactual awareness and sensitivity, experimental research has not confirmed these reports.

Driver performance and traffic safety

Because of the prominent role the automobile plays in our society, the possible implications of marihuana intoxication for traffic safety have been emphasized. Early reports were more optimistic about driver performance than recent evidence. Those consuming alcohol to the level of legal intoxication were originally found to make significantly more driving errors in a driving simulator situation than those who had consumed a "social dose" of marihuana. While the marihuana-intoxicated subjects indicated that their driving performance was affected, they felt they could compensate by driving more slowly and cautiously.

Present evidence, whether derived from driver test course performance, from actual traffic conditions or from the experimental study of components of the driving task, all indicate that driving under the influence of marihuana is hazardous (7–90). The increasing simultaneous use of both alcohol and marihuana by drivers poses a threat that may well exceed that of either substance alone. While the parameters of risk connected with the use of marihuana alone or in combination with alcohol prior to driving are not yet known, discouragement of

such use appears justified. A more accurate determination of the extent of risk involved in the various levels of intoxification would be desirable. Such studies are complicated by individual differences but are by no means impossible to execute.

Although there has been little systematic study of the relationship of marihuana smoking to possible pilot error, evidence related to driving is at least partially germane. Such skills as detection of peripheral stimuli and complex psychomotor coordination involved in driving are probably equally important in flying. In fact, the inherently greater complexity of flying suggests that performance is even more likely to be impaired under conditions of marihuana intoxication than is driving. Only one preliminary report of pilot performance has appeared in the research literature. This report indicates that under flight simulator test conditions experienced pilots show marked deterioration in their performance while marihuana intoxicated (7–108). More detailed studies are planned to better understand the nature of the performance deficits produced and their duration. A danger common to both driving and flying is that some perceptual or other deficits may persist for some time beyond the period of subjective intoxication. Under such circumstances an individual may attempt to fly or drive without realizing that his functioning is still impaired although he no longer feels "high."

Chronic use—special problem areas

Last year's report singled out several special problem areas involving potentially serious adverse consequences of chronic cannabis use. Subsequent research has not definitively resolved the questions raised but has expanded our knowledge base.

Some apparent inconsistencies in research findings regarding reduced plasma levels of the male hormone, testosterone, may be explained by the differing length of time users had been smoking before such levels were assessed. For example, the findings of one study that did not show a decrease during a several week period were matched by those in another study in which there were early negative findings. However, after four weeks elapsed a definite drop occurred (7–100). The decreases that have been found have still been within what are generally conceded to be normal limits. Their biological significance remains in considerable doubt. A preliminary finding that a marked reduction of sperm count (58%) occurred in five cannabis smokers following controlled conditions of smoking has been reported (7–171). While this poses the possibility of diminished fertility in chronic users, the small size of the sample and the study's preliminary nature make the work inconclusive.

With regard to hormonal aspects, two other adverse effects remain possibilities: (1) Interference with normal growth and sexual development of adolescent heavy users and, (2) Abnormal sexual differentiation of the male fetus developing in a mother who heavily uses marihuana during early pregnancy. No actual evidence for either of these speculative possibilities has yet appeared in the scientific literature.

The question of a cannabis induced impairment of the body's immune response remains important because of its potentially far reach-

ing clinical implications. While a number of investigators have published findings that suggest that marihuana may interfere with cell-mediated immunity, other investigators have not found such evidence. Some of these differences may reflect procedural variations; nevertheless, the clinical significance of the positive findings remains in considerable doubt. At least one study of experienced marihuana smokers under well-controlled, closed experimental ward conditions found initial evidence of impaired immunity upon their admission to the study. However, by the 63rd day of controlled cannabis administration, their immune response had apparently returned to normal (8–39). This finding suggests that the impairment of immunity initially detected in these and other marihuana smokers may be related to factors other than marihuana use.

The implications of laboratory findings of inhibition of DNA, RNA and protein synthesis, all basically related to cellular reproduction and metabolism, are at present unknown. These findings based on in vitro (outside the body) study of animal and human tissue cultures are also being followed up and extended.

Similarly, no conclusion evidence exists regarding damage to human genetic functioning (i.e., chromosomal damage produced by marihuana). While the most carefully controlled studies have failed to demonstrate such damage, the research to date must be regarded as insufficient to permit definitive conclusions.

Presently, preliminary evidence of a range of potentially serious consequences of marihuana use exists. As indicated, these include: Disruption of basic cell metabolism through interference with DNA and RNA synthesis, possible interference with pituitary function, in turn, affecting testosterone production and possibly having other endocrine effects and interference with the body's disease defenses by affecting the immune response. Despite this laboratory evidence, the clinical implications remain in doubt. While no evidence has appeared indicating that marihuana users here or abroad suffer from unusually high rates of infectious disease or cancer which might result from defects in the immune response, carefully controlled large scale clinical studies have not yet been conducted. Similarly, there is no evidence—but neither have there been adequate systematic studies—to establish whether users have significantly lower fertility rates or more serious problems with impotence than non-users.

The failure to detect gross clinical findings that might be expected does not, of course, mean that these issues have been resolved. To date systematic studies of matched samples have been modest in size. Detection of rarer consequences of use is less likely in studies of limited size and extent. As the number of chronically using Americans increases, larger scale epidemiological studies are becoming feasible. Plans for such studies are underway.

OTHER CHRONIC HUMAN EFFECTS

Tolerance and dependence

Tolerance to cannabis—diminished response to a given repeated drug dose—has been substantiated by research evidence. Development of tolerance to marihuana's effects was originally suspected because

of the obvious ability of cannabis users overseas to ingest larger quantities of the drug without disruptive effects than was possible for less experienced American users. Systematic, controlled studies in which known doses of marihuana or THC were administered over extended periods have now confirmed this (8–53, 80, 109, 111).

The meaning of cannabis dependence is often somewhat vague. If we define it as a physical dependency manifested by physical symptoms following drug withdrawal, there is now evidence that it can occur. The symptoms that have been reported following discontinuance of high dose chronic administration of delta-9-THC include: Irritability, restlessness, decreased appetite, sleep disturbance, sweating, tremor, nausea, vomiting and diarrhea (8–80). It should be noted, however, that the after effects reported followed unusually high doses of orally administered THC under research ward conditions. Such changes have not commonly been observed in other studies nor has a "withdrawal syndrome" typically been found among users here or abroad.

Psychopathological and neurological aspects

The question of possible prolonged behavioral effects of chronic cannabis usage has been an area of fundamental concern throughout the American cannabis research program. As indicated in earlier reports, foreign observers have argued that a range of such effects occurs, including a specific cannabis psychosis, diminished intellectual performance and an "amotivational syndrome" (characterized by a loss of interest in work and other conventional activity). Interpretation of such reports has unfortunately been complicated by the lack of adequate control groups, poor research design, use of opium and other drugs, poor diagnostic criteria, nutritional deficiencies and other differing factors of life style.

Even when a particular consequence is correlated with marihuana use, it is often erroneously attributed to the drug use. A recent study of 38 first admissions to a psychiatric hospital illustrates the problem of interpretation involved: While there was a correlation between marihuana and subsequent psychiatric illness, it was less than with such causally unrelated variables as having danced and having drunk beer (7–2).

The acute panic anxiety reaction, previously mentioned in the discussion of acute effects, is probably the most common adverse reaction. However, a more prolonged cannabis psychosis has been reported in Eastern literature. It appears to occur under conditions of unusually heavy use or as a result of ingesting a larger amount than usual. Descriptions do not always distinguish between an acute brain syndrome or toxic delirium marked by clouded mental processes, disorientation, confusion and marked memory impairment and a more prolonged psychotic reaction precipitated by cannabis use. Often it is difficult to isolate the causative role of marihuana from that of pre-existing psychopathology or other drug use (7–64, 112).

Three NIDA-supported research studies of heavy chronic users conducted in Jamaica, Greece and Costa Rica have failed to detect evidence for a cannabis psychosis. However, given the comparative rarity of this syndrome and the small sample sizes used, it is possible that such a consequence was missed.

Studies of college student performance have generally failed to prove evidence of impaired intellectual performance related to marihuana use.

While there was no evidence of differences in grade point average or in educational achievement, marihuana users in one major study had greater difficulties than non-users in deciding career goals and were more likely to have dropped out of college to reassess their goals (7–11). Some of these studies suffer from several shortcomings, however; the samples studied may not have adequately emphasized college drop-outs thus excluding the very group that might have been most adversely affected by heavy use. A second consideration is that students typically have higher levels of ability than the general population. Particularly in more competitive academic environment, they may have above average motivation allowing them to better compensate for cannabis effects. Finally, even moderately heavy American student users use the drug less frequently, in less potent forms and in lesser quantity than more heavily using overseas populations.

Assessing the psychosocial effects of marihuana use in chronically using populations can be complicated. Changes in values and behavior attributed to marihuana use may, in fact, have preceded use rather than the use affecting the change in values. Especially in earlier years, users were much more likely to hold counterculture, antiestablishment views. For these users marihuana had symbolic value as a means of indicating their disdain for the prevailing value system. This disdain was frequently accompanied by a rejection of the traditional work ethic with its emphasis on competitive achievement. The group dynamics of marihuana use may, however, reinforce these counterculture views of more conventional motivation rather than result from any pharmacological action of the drug itself.

Similarly, attempts to create experimental models for testing the existence of such an "amotivational syndrome" have had serious limitations. Tasks chosen as tests may significantly depart from more realistic work tasks; the artificial environment if the research setting may not provide more typical motivational conditions. Two studies involving marihuana administration coupled with monetary reward for work performance did find a decline in productivity with heavier marihuana consumption. In one the task was simple and relatively undemanding, involving repetitive button pushing that could be carried on simultaneously with other activity (7–111). In the other, a more typical work task—the making of wooden stools—was carried on (7–13). The distinction between a direct effect on performance as a result of marihuana and on performance as a result of a decline in motivation is not easily made, however. In a third, quite limited study of agricultural performance undertaken in connection with the Jamaican study of chronic users, researchers found some decline in work performance although the decline was not dramatic (7–141).

When one turns to the neurological evidence there is little question that there are acute effects of marihuana intoxication although these are not easily distinguished from those of other psychoactive drugs as measured by conventional electroencephalograms. The EEG changes resulting from electrodes implanted deeply in the brain are dissimilar to other psychoactive drugs (7–67). The behavioral significance of the

EEG changes that have been found in chronically using monkeys and in very limited human studies is not presently known.

Work in Greece has not supported previously cited evidence suggesting that brain damage marked by enlarged ventricles may result from marihuana use. The Grecian study, using noninvasive echo-encephalographic techniques for measurement of ventricle enlargement, found no evidence of such brain damage in heavily hashish using men matched with non-using controls (7–49).

Field studies of chronic users

Although other portions of this and previous reports touch on one or another of the three Federally sponsored studies of chronic marihuana use in Jamaica, Greece and Costa Rica, it may be useful to summarize their findings, strengths and weaknesses here. The Jamaican study has been extensively reported in previous Marihuana and Health reports, a recently published book and in the research literature (7–141). A report on the Greek study was delayed in order to make the data base as complete as possible. The third study in Costa Rica was just completed; its detailed findings will be released by Spring, 1976. In each of these research efforts, an attempt was made to match drug-using subjects with appropriate nonusing counterparts. In the Jamaican and Costa Rican projects rather careful matching was done; in the Greek study such matching was less possible. All subjects were males because male use predominates in the cultures studied. Numbers of subjects were necessarily limited by the detailed procedures followed (Jamaica: 30 experimental, 30 control; Greece: 47 experimental, 40 control; Costa Rica: 40 experimental, 40 control, although 80 and 140 users and non-users respectively were actually examined).

The Jamaican study found few physiological or psychological differences between the matched smoker nonsmoker populations. A rather extensive battery of tests of physical and psychological functioning found no differences that could be directly attributed to marihuana use as such. While an attempt was also made to assess chromosomal abnormalities, that portion of the study must be regarded as inconclusive because of technical deficiencies in the methodology for that phase of the project.

The Greek study arose from a clinical impression by Greek observers that Greek hashish users, because of their heavy use patterns and already established researcher-subject rapport, would make a good study population for examining the effects of unusually heavy cannabis use.

A variety of neurological, psychological and physical measures found few changes attributable to cannabis use. Heavy emphasis was placed on possible brain damage as measured by electroencephalographic, echo-encephalographic (Cf. preceding section) and psychological test procedures. None of these measures showed evidence of brain damage (7–49).

The most recent Costa Rican study also examined matched samples of users and non-users especially carefully matched on such variables as age, marital status, education, tabocca smoking and alcohol use. Emphasis was placed on extensive medical examinations with special attention to pulmonary and neuropsychological functioning. Although

detailed results have not yet been published, no evidence for a greater incidence of disease or of psychological deterioration has been found in the cannabis-using group (7–23).

None of the three studies found evidence of increased psychopathology or of an amotivational syndrome stemming from the use of cannabis.

While results of these studies must be regarded as somewhat reassuring of the lack of grossly adverse consequences of marihuana use, they can not, of course, be regarded as conclusive for several reasons. All three studies involve relatively small numbers of subjects. Equally limited studies of cigarette smoking, for example, which is known to have serious adverse health consequences, would not have been likely to detect those consequences. Psychological testing techniques are less apt to be satisfactory when used with subjects markedly different from the original standardization samples. To the extent that they are not culture free, performance for both experimental and control groups in cultures unlike those on which they were standardized may both show a culturally derived deficit. This deficit may mask a drug-related deficit in performance. Thus, the tests used may not be sufficiently sensitive to detect a difference that may in fact exist. Finally, it may be argued that the demands of a less technologically oriented society are less complex than those of the industrialized United States. Thus, the failure to find a drug-related decrement in social or work performance may reflect an unimpaired ability to meet the demands of a simpler situation that would not be true under more demanding circumstances.

THERAPEUTIC ASPECTS

Although cannabis has been used for over 3,000 years as a medicinal herb in native and scientific medicine, its use in Western medicine sharply declined in modern times. By the 1930s, American medicine had largely supplanted cannabis with more convenient and more stable pharmaceutical preparations. Our relatively recent concern with marihuana as a drug of abuse has led to scientific investigation into its properties by means of modern pharmacological techniques. Synthesized constituents of the natural material have been produced enabling researchers to study the properties and effects of each of the components of this complex material. This recent study has reawakened scientific interest in possible therapeutic uses for the natural material or its synthesized ingredients.

Although some of marihuana's properties—notably its psychoactivity and its tendency to accelerate heart rate—are undesirable for most medicinal purposes, cannabis has one highly desirable property. Compared to most pharmaceuticals it is very low in biological toxicity. Indeed, it is questionable whether any deaths can be directly attributed to an overdose of marihuana or hashish.

Whether or not cannabis or perhaps some modified constituent again becomes useful in medical practice will depend on whether some of the drug's promising therapeutic properties prove to be sufficiently persistent and its side effects controllable. Marihuana's usefulness as a medication for chronic disorders may also prove to be limited by the development of tolerance to its therapeutic effects.

The most promising therapeutic applications of the drug are in the treatment of glaucoma, as an anti-emetic for cancer patients receiving chemotherapy and possibly in the treatment of asthmatics. Other applications as a sedative-hypnotic, an anticonvulsant, an antidepressant, an analgesic and in connection with the treatment of alcoholics have been attempted, but the results have either been inconsistent or highly preliminary.

The use of cannabis and THC in treating the elevated intraocular pressures in glaucoma patients arose from the observation in normals that internal eye pressures were reduced by the drug. Subsequent research with patients has confirmed that the effect is also produced in the diseased eye and is as great as that produced by more traditional medications. Topical preparations applied to the eyes of rabbits have successfully reduced pressure raising the possibility of using such a preparation with humans. Human experimentation is not, however, expected in the immediate future because of the formidable problems in making certain that such a preparation is safe and can meet regulatory requirements (9–12, 25, 26).

The use of THC as an anti-emetic with cancer patients receiving chemotherapy shows unusual promise. One of the undesirable side effects of chemotherapeutic agents administered to cancer patients is that they produce marked nausea and vomiting. This side effect is very difficult for patients to tolerate and is also debilitating. Standard anti-emetic drugs have not, unfortunately, been notably successful in reducing this side effect. THC, by contrast, was found in a recent double-blind study (neither patient nor physican knew whether the drug received was active or inert) to be effective in virtually all of the patients receiving it. While 13 of the 16 patients receiving the drug became "high" and one third developed drowsiness, these effects were viewed as minor compared to the therapeutic benefit achieved (9–58).

Use of THC in the treatment of asthmatics is predicated on the observation that it dilates pulmonary air passages and decreases airway resistance (9–64). Based on observations in normal research with asthmatics has demonstrated that marihuana relieves bronchospasm and has a more persistent action than traditional medication (9–65). Since smoked marihuana has obvious lung irritant properties, more recent research has employed aerosolized THC, also with promising results (9–46).

There has been a growing awareness that constituents other than delta-9-THC may have valuable therapeutic properties if freed of some of the undesirable side effects noted with THC. It is also possible for the organic chemist to produce a very wide range of chemical compounds which are broadly based on the chemical structure of the cannabinoids, but with changes in that structure which can markedly alter their action. Such chemically more remote compounds may ultimately prove more useful therapeutically than either the natural material itself or its synthesized ingredients. Because they are not the parent compounds they must, of course, be carefully tested for toxicity and therapeutic properties like any other new compound.

CHAPTER 1

Epidemiology of Marihuana Use

PRESENT PATTERNS AND CHANGES IN USE

National household surveys (adult)

The National Commission on Marihuana and Drug Abuse sponsored national household surveys of marihuana and other drug use in 1971 and 1972 (2, 3). A third national survey conducted in late 1974—early 1975 provides a comparison with the earlier periods (1). (See Table A–1)

Another national survey conducted for the Drug Abuse Council in 1974 found very similar results. The percentages of adults (18 and over) reporting ever having used and currently using were 18 and 8% respectively (24). As can be seen in Table A–1, the number of adults currently using marihuana has not changed appreciably in the past two years. Usage continues to be concentrated in the 18–25 age bracket and is about twice as frequent for males as females.

Current usage is about equal for white and non-white groups. It is positively associated with education, and is highest for those now in college (33%). Current usage continues to be highest in the West (11%) and lowest in the South (4%), and higher in large metropolitan areas (9%) than in non-metropolitan regions (3%). However, all of these differences have become less pronounced in the past three years.

Because of the relatively small numbers involved, national general population surveys do not provide very accurate estimates of changes in heavy marihuana use; nevertheless, some information is available. The 1971 Marihuana Commission survey reported daily or more frequent use among adults at 0.5%, while the comparable value for 1972 was 1.4%. The follow-on survey in 1974 did not report the rate of daily use, but noted that adult usage of nine or more days in the past month was 2.7%. The 1974 Drug Abuse Council national survey reported 1.5% of the adult sample used marihuana daily or more frequently. These limited data do not appear to indicate a change in adult daily usage in the past two years.

National household surveys (youth)

The results of the Marihuana Commission surveys of youth ages 12–17 and the results of the 1974 follow-on study are found in Table A–2.

TABLE A-1.—MARIHUANA USE AMONG ADULTS, 1971–74 (1, 2, 3)

	Percent ever used			Percent current use [1]		
	1971	1972	1974	1971	1972	1974
All adults	15	16	19	5	8	7
Age:						
18 to 25	39	48	53	17	28	25
26 to 30	19	20	29	5		
35 to 49	9	6	7	1	1	1
50 plus	6	2	2			
Sex:						
Male	21	22	24	7	11	9
Female	10	10	14	3	5	5

[1] Used during last month.

TABLE A-2.—MARIHUANA USE AMONG YOUTH, 1971–74 (1, 2, 3)

	Percent ever used			Percent current use [1]		
	1971	1972	1974	1971	1972	1974
All youth	14	14	23	6	7	12
Age:						
12 to 13	6	4	6	2	1	2
14 to 15	10	10	22	7	6	12
16 to 17	27	29	39	10	16	20
Sex:						
Male	14	15	24	7	9	12
Female	14	13	21	5	6	11

[1] Used during last month.

Another set of national household data collected in a Columbia University study reported quite similar results (8, 16):

	Percent ever used
Age 12 to 17:	
1971	15
1972	15
1973	17
1974 to 1975	22
Age 16 to 17:	
1971	28
1972	31
1973	32
1974 to 1975	40

However, the 1974 national survey conducted for the Drug Abuse Council reported considerably lower marihuana usage for 12–17 age group, 14% in the "ever used" category and 5% as "currently using" (24). This discrepancy may have been related to the relatively small sample size of 505. This survey also utilized "rider questions" attached to a larger unrelated survey.

The Marihuana Commission surveys in 1971 and 1972 reported daily marihuana usage for the 12–17 age group at 0.6% and 1.3% respectively. The follow-on 1974 survey found 4.4% indicated usage of nine or more times in the past month. The 1974–75 national survey for the Columbia University study found 2% of youth ages 12–17 and 4% of those either 16 or 17 years of age reported using marihuana 60 or more times within the two-month period. While the percentage of daily use was not reported for the earlier years, the 1974 Drug Abuse Council survey reported daily or more frequent usage by 1% of 12–17 age group and 3% of those 16–17.

Student surveys

A longitudinal study of high school males followed from their senior year to five years after graduation provides an indication of changes in marihuana usage over time in the same group (14, 15). The sample of over 2,000 was selected from 87 public high schools so as to be representative of American males entering high school in 1966. (Data arrayed in Table A–3.)

Another study surveyed drug usage in 22 selected high schools throughout the United States in 1971 and 1973 (16). These data are not necessarily representative of the student population, but do provide an indication of changes in marihuana use over the two-year period. (Table A–4)

A survey of 16,000 male and female high school seniors in 130 schools, selected to be representative of public and private high schools throughout the country, was conducted in 1975 (15) and is to be repeated on an annual basis. The percentage of high school seniors reporting marihuana usage in the 1975 survey were:

TABLE A–3.—PERCENTAGE OF MARIHUANA USE AMONG A NATIONAL SAMPLE OF HIGH SCHOOL MALES (14, 15)

	Senior year, 1969	1 year after graduation, 1970	5 years after graduation, 1974
Ever used	20	35	62
Any use in prior year	20	33	52
Daily or weekly sometime in prior year	6	9	21
Daily use sometime in prior year	1	2	9

TABLE A–4.—PERCENTAGE OF MARIHUANA USE REPORTED IN 22 HIGH SCHOOLS (16)

	Junior high school		Senior high school	
	1971	1973	1971	1973
Ever used	15	19	38	48
Ever used 60 or more times	2	4	11	17
Used in past 2 months	11	13	27	36
Used 60 or more times in past 2 months	1	1	2	4

	Percent
Ever used	47
Used in last 12 months	41
Used in last month	29
Used 20 or more times in last month	6

The only regularly conducted national survey of marihuana use among college students is that prepared by Gallup (9). The percentages reporting having ever used this substance in surveys conducted between 1967 and 1974 were:

	Percent
1967	5
1969	22
1970	42
1971	51
1974	55

One other national student survey conducted in 1974–75 for Drug Abuse Council found 48% of high school and 64% of college students

reported having used marihuana (33, 34). The corresponding percentages for daily use were 6% and 8%.

One local survey of particular interest is that annually conducted among high school students in San Mateo County, California since 1968 (4). Table A–5 shows the percentage of ninth and twelfth grade male students reporting one or more, ten or more, and 50 or more uses of marihuana during the preceding year.

San Mateo County is adjacent to San Francisco, and thus had an earlier and more pronounced exposure to the counterculture movement and associated drug use than did most other areas. This is particularly evident in the figures for the late 1960's. For instance, one year after Gallup found only 5% of nationwide college students had used marihuana (1967), the comparable percentage for senior males in San Mateo county high schools was 45%. The percentage of San Mateo students using marihuana in 1975 is still substantially above the national level; however, the difference is not nearly so large. It is interesting to speculate on the meaning of this narowing gap. One possibility is that the apparent plateau may be a ceiling and that the growth of marihuana use in San Mateo may have reached its limit. It may also be that other drugs (viz cocaine), not of great interest when the study began in 1967, are now luring users away from marihuana. Many alternative explanations for the San Mateo phenomenon are possible; whether the phenomenon or its alternate interpretations have any meaning for the national level is unknown.

In summary, at the national level marihuana use appears to have significantly increased among youth during the past two years. This is indicated by the trend in national household surveys as well as surveys of various high school student populations. This conclusion is contrary to that suggested in the 1974 Marihuana and Health report, when data available at that time seemed to indicate a plateau had been reached (20). It also appears that daily marihuana use has increased among youth, although the available data on changes in daily use are fairly limited.

TABLE A–5.—PERCENTAGE OF MARIHUANA USE AMONG MALE SAN MATEO COUNTY HIGH SCHOOL STUDENTS (4)

	1 or more uses in past year		10 or more uses in past year		50 or more uses in past year	
	9th grade	12th grade	9th grade	12th grade	9th grade	12th grade
1968	27	45	14	26	NA	NA
1969	35	50	20	34	NA	NA
1970	34	51	20	34	11	22
1971	44	59	26	43	17	32
1972	44	61	27	45	16	32
1973	51	61	32	45	20	32
1974	49	62	30	47	20	34
1975	49	64	30	45	20	31

Marihuana use among males, age 20 to 30

One of the most significant recent studies involved the interviewing of 2,500 selected to be representative of the 19,000,000 U.S. males in the 20–30 age group (23). This group evidences the highest rate of drug use, and the in-depth interviewing of a relatively large representative

sample provided more reliable information on marihuana and other drug-using behavior than had previously been available.

The data were collected from October, 1974 to May, 1975 and showed that 55% of those interviewed had at some time used marihuana. Defining as current use any use in the year 1974–1975, the study reported 38% current users. Fifteen percent reported having used marihuana daily or almost daily at some time. Eleven percent reported using marihuana 1,000 or more times, and 11% also reported use within 24 hours of the interview. Hashish use at some time was reported by 29%, and the use of hashish oil by 11%. Surprisingly, 11% of the total sample and 41% of those described as heavy users reported growing marihuana for their own use.

When particular age categories within this group are examined, the data show that 37% of the men who were 29–30 at the time of the interview had used marihuana in comparison to 63% of the 20–24 age group. When those described as light or experimental marihuana users are excluded, the differences are even more striking: 12% of those 29–30 reported use in comparison to 37% of those 20–24. These results indicate that males now in their late twenties are less likely to have tried marihuana than men five to ten years younger, and are considerably less likely to adopt marihuana use as a frequent behavior. Similar or more pronounced differences probably exist for those over 30. For instance, the 1974 follow-on to the Marihuana Commission Survey found 7% of males and females aged 34–49 reported having used marihuana, but only 1% had done so within the past month.

The peak year of first marihuana use for the sample of males between 20 and 30 was 1969; however, the peak year for any use during the calendar year was 1974 when the rate for this group reached 37%. The authors concluded that the data were clearly consistent with an upward trend in marihuana use.

This study also revealed that the differences in marihuana use as a function of various demographic characteristics were not as pronounced in the group sampled as those reported in the general population. In the male 20–30 age group, 70% of those living in cities of over 1,000,000 population had used marihuana in comparison to 43% of those in communities of less than 2,500. In terms of education, the percentage reporting some use of marihuana was almost identical for those with less than high school education, high school graduates and college graduates. Those who had attended college without graduating showed a higher rate. For those aged 20–23 at the time of the interview, the percent having used marihuana was virtually the same for those still in school and those not. A higher percentage of blacks (65%) than whites (54%) reported some use, but the inverse relation of marihuana use to age was not as apparent in the black group. Blacks and other ethnic minorities showed a higher prevalence of marihuana use prior to the late 1960s, but minority youth were less influenced by the recent epidemic (5).

A synthesis

The overall survey results indicate that marihuana use has not significantly penetrated the portion of the adult population over 30 years of age. Where use has occurred in this group, the frequency has been

mostly of an experimental nature. However, the plateau in current marihuana use among adults found in national survey results may be deceptive in predicting future usage. As the more frequently using younger groups enter the adult age range, the overall rates are likely to increase.

Results from both household surveys and student studies indicate that marihuana use is still increasing among youth at the national level, although usage appears to have stabilized in certain areas which reached a relatively high level in the early 1970's. Most of the data on youth also indicate that daily or near-daily usage has increased in the past two to four years.

If recent marihuana usage in the United States is compared with that prior to the epidemic which began in the late 1960's or especially with patterns of use in countries where cannabis use has been indigenous for many years, some useful perspectives emerge. It is clear that much of the recent American usage is quite minimal, both in terms of frequency of use and amount consumed (21, 27). The patterns of use often seem to be based more on the adoption of a fad or style than an attraction to the pharmacological properties of the drug. This is not to say that, once it is introduced as a fad, marihuana use will not be sustained because of its pharmacological effects.

Based on currently available survey data, it appears that around 2% of youth, aged 12–17 or about 8% of those who have tried it, are currently using marihuana daily. For those 17 years-of-age, around 4 or 5% are probably daily users and for 17-year-old males the percentage is of the order of 6 or 7%, or about 13% of those having tried it.

For adults, the overall daily use is probably only 1 or 2%, but a more meaningful percentage is that for the age groups primarily involved. As described earlier, the percentage of daily use among males 20–30 years of age is around 8 or 9% or 15% of those who have tried marihuana. For males 20–24 years of age, current daily use is around 10 or 11%, or about 17% of those having ever used the drug.

SOCIAL AND PSYCHOLOGICAL CORRELATES

Research on the social and psychological correlates of marihuana use may be organized under three headings: 1) pre-use characteristics; 2) factors influencing transition from non-use to use, including the temporal order of drug-using behavior; and 3) correlates of marihuana use following its adoption. In most instances only statistical associations, as opposed to casual relationships, can be established.

Pre-use characteristics

This aspect has been thoroughly covered in earlier research and recent work has largely served to confirm prior findings. Aside from the association of marihuana with routine demographic variables such as those mentioned in the previous section, the majority of variables which predict marihuana use, ranging from a break with traditional values (7, 10, 19) to more severe behavioral and adjustment problems (11) are related to lack of conformity. Smith has found self and peer

ratings of rebelliousness to be among the best predictors of high school students who subsequently become marihuana users (29).

Factors influencing transition from non-use to use

In a longitudinal study of high school students, Jessor has shown that those individuals who will initiate marihuana use can be identified with considerable accuracy from various personality, belief and attitude measures (13). Furthermore, these measures, such as attitude toward deviance, value of achievement and friends' approval of drug use, show significant changes in the direction of the user group during the period of marihuana initiation. Jessor has found similar results with regard to the initiation of alcohol drinking and sexual behavior.

Several studies have investigated the role of child-rearing practices and parents' drug-using behavior in the initiation of adolescent drug use. One recent study found that perceived laissez-faire parent-child relationships led to high marihuana usage among the offspring; an autocratic relationship led to medium usage; and quasi-democratic or democratic relationship led to low usage (12). Another study found higher rates of marihuana use when the parents showed less disapproval of use, and also when the father used prescription drugs (25). Kandel also found a positive relationship between parents' drug-using behavior and the child's marihuana use, although her work demonstrated rather conclusively that this effect was minor in comparison to peer group influence (17). This emphasis on peer influence is in accord with the thesis of Suchman and others that student marihuana and other drug use is largely determined by the integration into a social subculture in which drug use is a part (31, 32).

One social environment, the military, has apparently proved to have less influence on marihuana and other drug use than was initially believed. O'Donnell, et al., in their study of 20–30 year old males found that neither domestic nor overseas service had any effect on marihuana use (23). Robins has also found that Vietnam veterans' marihuana use after return was not significantly increased over that for a comparison group who did not enter the military (26).

Since marihuana use is known to generally precede other illict drug usage, the question is often raised as to the role of marihuana in facilitating the transition or progression to more dangerous drugs. While not specifically answering this question, Kandel and associates have determined that the temporal sequence along the legal-illegal drug continuum is consistent (18, 28). By conducting longitudinal studies of two large samples of high school students, they were able to determine the order in which the various drugs were used. Only 1% of the sample began using illicit drugs without first using a legal drug. Beer and wine collectively constituted by far the most common "entry drug" (28%) with cigarettes accounting for 6% and hard liquor 3%. In addition to the fact that legal drug use virtually always preceded illicit use, heavy use of both liquor (weekly) and cigarettes (over a pack a day) resulted in a high percentage (40%) moving from non-use to use of illicit drugs in a five month period. Only 2 to 3% of adolescent legal drug users progressed to other illicit drugs without first trying marihuana. If the individual progressed beyond marihuana, the next step

was generally pills. Subsequent steps were psychedelics, cocaine and heroin, in that order; but, of course, only a small percentage progressed to the higher levels in the sequence. Heavy use of marihuana or other drugs along the sequence was more often followed by progression to the next step, and also by a higher probability of moving two or more steps during a single time period.

Correlates of marihuana use

Although marihuana use has become increasingly common over the past several years, it is not surprising that those who are less conventional in other respects are more likely to use the drug than are the more traditionally oriented. In their national study of males, ages 20–30, O'Donnell et al., found that those men living in consensual unions (i.e., with a woman to whom they are not married) were more likely to be using marihuana than those living independently, or living in their parental home. Those who were married and living with their wives were least likely to be using the drug (the percentages of current use in ascending order were: married, 25%; living with parents, 38%; living independently, 56%; consensual union, 68%). A similar trend was found in the use of other drugs including alcohol and tobacco (i.e., current drug use of all types was greater by males in consensual unions than among those who were married). Those unemployed at the time of interview were more likely to have used marihuana in some time in their lives than those who were employed (72% of the unemployed had ever used compared to 52% of the employed) (23).

In this same study both self-reported criminal acts and contacts with the criminal justice system (some drug use related) were substantially higher for marihuana users than for the non-users. The authors caution, however, that "the fact that drug use sometimes occurs first and at other times criminal behavior precedes use indicated that if there is a causal connection between drug use and criminal behavior, it is not a simple one" (23). Similar results have been reported in terms of arrests by Brill and Christie (1% for non-users compared to 10% for regular marihuana users) (6).

An Air Force study of some 4500 men reporting marihuana use indicated somewhat poorer performance when compared with a control group of non-users (22). Finally, a longitudinal study of college freshmen found a strong relationship between marihuana and other drug use and the choice of unconventional careers (30). There was also a disproportionate tendency for marihuana users to change in the direction of unconventional careers during the two-and-one-half year follow-up period and the authors concluded, after multivariate analysis, that the results suggest a causal relationship. However, it should be stressed that, in general, studies relating marihuana use to other variables have not established more than a statistical association. It is clear that marihuana usage is frequently part of a larger pattern of nonconformity, but the existence of causal relationships between marihuana use and other behavior have generally not been determined.

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CHAPTER 2

Chemistry and Metabolism

Because the drug abuse problem involves marihuana, the study of the pharmacological and toxicological properties of the drug must be pursued; cannabis, however, is a complex mixture of variable amounts of numerous, potentially active substances. The chemistry of marihuana is, therefore, of paramount importance to the investigator, and the recently reported development of relatively simple analytical procedures for the separation and quantitation of the major cannabinoids in marihuana is a significant advance. The effects of marihuana can now begin to be more meaningfully compared in different laboratories, and many of the past problems of conflicting data will be avoided simply by knowing the chemical composition of the sample at hand. Indeed, the United Nations has recommended that all research reports on the properties of marihuana include a quantitative account of the major cannabinoid content of the preparation involved.

Another notable contribution in the field of cannabinoid chemistry was the introduction of a refinement in the synthesis of delta-9-THC, the major psychoactive drug in cannabis. In recent years, the synthesis of delta-9-THC, as well as of other cannabinoids, has been subjected to extensive investigation, which has resulted in a continuous simplification of the synthetic procedures. Such developments have reduced the cost of synthesis and thereby increased the availability of these important drugs for scientific investigation. The long-term significance of the recent refinement must be viewed in the perspective of a long list of many contributions to our understanding of the chemistry of cannabis and its constituents. In the past few years the chemical study of cannabis has resulted in the isolation, characterization and synthesis of numerous constituents of marihuana, thus providing biologists with the opportunity to study the pure drugs. In a classical sense, the chemical advances represent the basis for the rational investigation of the pharmacology and toxicology of marihuana.

New reports of the isolation and identification of some of the metabolites of marihuana continue to represent the most important aspect of research in the area of metabolism. In the human, for example, cannabinol has now been reported as a metabolite, and several new ones have been isolated from urine. It is essential to pursue the identification of marihuana metabolites because the question of what accounts for the pharmacological and toxicological activity of marihuana can only be answered by a study of the constituents of cannabis and their respective metabolites. The importance of metabolism was first demonstrated a few years ago when 11-hydroxy-delta-9-THC, a major metabolite of delta-9-THC, was found to be as active as, or more

active than, the parent compound. In the current Marihuana and Health report, the study of the anticonvulsant activity of the cannabinoids has revealed that another metabolite, 8-alpha, 11-dihydroxy-delta-9-THC, is also a very active substance. It is not unreasonable to assume that still other marihuana metabolites will be found to produce significant pharmacological and toxicological effects.

DRUG SOURCES

The detailed chemical analysis of cannabis has been extended to yield more components (4, 43, 44), and investigators have recently identified a new spermidine alkaloid called cannabisativine in an alcoholic extract of the root of *Cannabis sativa* L. (24).

The importance of the influence of smoking marihuana on the nature of its chemical constituents continues to be recognized (14, 18, 19, 20, 37). A detailed analysis of the pyrolytic products of cannabidiol (CBD) has demonstrated that one of the principal volatile products formed is olivetol, a pharmacologically active chemical precursor of the cannabinoids (19).

The cannabinoids are potentially unstable compounds and their stability in chloroform, a commonly used solvent for extraction and storage of cannabinoids, has been re-examined (51) : The results of a three-month storage study support a previous assessment that either synthetic or naturally occurring cannabinoid mixtures are reasonably stable. Other investigators have determined the influence of pH on stability by describing the kinetics of the degradation of delta-9- and delta-8-tetrahydrocannabinol (delta-9-THC, delta-8-THC) at different pH values (12).

More new cannabinoids have been synthesized and examined for pharmacological activity (8, 22, 52), and the synthesis of delta-9-THC has continued to be refined with the introduction of a one-step reaction using either chrysanthenol (35) or p-mentha-2,8-dien-1-ol and olivetol (34).

ANALYTICAL TECHNIQUES: DETECTION

At the present time four principal methods are used for the analysis of cannabinoids: gas-liquid chromatography (GLC), thin-layer chromatography (TLC), mass spectroscopy (MS) and radioimmunoassay (RIA). The chromatographic procedures remain the most useful because they offer either simplicity, as in the case of TLC, or the best combination of sensitivity and selectivity, as in the case of GLC. The GLC methods have been especially useful in the separation and quantitation of cannabis constituents (31). One of these methods, which involves the formation of silyl derivatives of 2% OV–17 chromatography columns (49), has been extremely valuable for the elucidation of the major components of cannabis. This method, referred to in the 1974 Marihuana and Health report (25), demonstrated that previous GLC analyses of cannabis failed to separate CBD from cannabichromene (CBC) ; hence, some CBD samples used in pharmacological studies were probably significantly contaminated with CBC. The recognition of the prevalence of CBC in some cannabis samples should prompt a re-evaluation of the pharmacological effects of pure CBD and an evalu-

ation of the pharmacological properties of CBC, alone and in combination with CBD.

The variability in cannabis composition has led the United Nations to recommend that all scholarly reports on the effects of cannabis include a quantitative analysis for CBD, cannabinol (CBN), and delta-9-THC content; the GLC method described above was recommended for this purpose. Subsequently, the same research group published another GLC method which does not require derivatization, but still provides satisfactory separation of CBD and CBC (50). The relative simplicity of this procedure suggests that it is the current method of choice for the analysis of cannabis for its principal cannabinoid constituents.

New TLC methods for the cannabinoids continue to be developed (9, 16, 17, 29, 48). A two-dimensional TLC system has been described as capable of separating 27 constituents of hashish resin, including CBD, CBN, delta-9-THC and CBC (29). This technique uses silica-gel plates and the solvents n-pentane-diethyl ether-ethyl acetate (90 : 8 : 2) and n-pentane-aceton (90 : 10). In another report a new procedure for extracting urine enables the cannabinoid metabolites to be separated into neutral, weak and strong acid fractions, which can be easily fractionated further by TLC (17). In addition, the use of methanol to extract delta-9-THC and its metabolites from tissues was found to yield higher recoveries than other common extraction methods (38). Finally, the factors that influence the stability and color intensity of the chromogen-cannabinoid products have been identified as chromogen basicity, residual solvent and chromogen dyestuff (9).

High pressure liquid chromatography (HPLC) represents a new and potentially useful technique for cannabinoid analyses. The great separatory capability inherent in HPLC should lend itself well to the general problem of resolving complex cannabinoid mixtures. A recent report has described the use of dansyl derivatives for the fluorometric detection of cannabinoids separated by HPLC (1). The results obtained from the analysis of cannabinoid standards illustrate that the combination of dansyl derivatives and HPLC provides a method with the sensitivity and selectivity of GLC and mass fragmentography. This method has recently been used effectively in an examination of cannabinoid metabolites in dog feces (23). Furthermore, it is interesting to note that HPLC has been used to separate quantitatively delta-9-THC from other plasma heptane extractable substances (e.g., lipids) that can interfere with the GLC analysis of such extracts (11).

Since the pioneer mass spectroscopy work with cannabinoids by Agurell, et al. (56), which was summarized in the fourth Marihuana and Health report (25), the technique has played an important role in the identification of individual cannabinoids. The inherent sensitivity of the technique lends itself well to the potential measurement of cannabinoids in biological samples; and workers at the Research Triangle Institute have developed a method for the quantitative analysis of human plasma for concentrations of delta-9-THC as low as 0.5 ng/ml (58). Mass fragmentographic methods have also been used in a number of other studies (16, 23, 29, 43, 44, 57).

Several reports have also appeared describing the use of RIA for the detection af cannabinoids, particularly in body fluids (13, 26, 46, 47).

In addition, two new immunoassay techniques are under consideration: homogeneous enzyme immunoassay (36) and free radical immunoassay (6). The most appealing feature of immunoassay is its great sensitivity, but limited selectivity continues to restrict its applicability.

METABOLISM

The continuing study of the biological disposition of the cannabinoids has yielded a greater understanding of factors affecting their metabolism, the nature of their metabolites, their distribution in the body and, finally, the routes of their excretion. Research into hepatic microsomal metabolism was designed to define the optimal in vitro conditions for the metabolism of delta-9-THC (40). The influence of several cannabinoid vehicles on delta-9-THC metabolism was evaluated, and apparent Km and Vmax values were determined. The pattern of metabolite production was followed as a function of duration of incubation.

Twenty-four hours after oral administration, crude cannabis resin was found to increase both pulmonary and hepatic aryl hydrocarbon hydroxylase activity in male rats (42). The stimulus for this effect may have been the trace quantities of benzo-(alpha)-pyrene found in cannabis resin. In another experiment, the rate of delta-9-THC metabolism both in vivo and in vitro was increased by the daily pretreatment of rats with phenobarbital (39). Despite an increased rate of metabolism, neither the apparent Km nor Vmax was altered. The phenobarbital effect was compared with the response in tolerant animals: In vitro, the rate and pattern of metabolism was unchanged, and, in vivo, the amounts of cannabinoid in tissue and its disappearance from blood was also unaffected. The data suggest a functional, rather than a dispositional, basis for tolerance.

Various drugs have been examined in terms of their effects on the in vitro and in vivo metabolism of delta-9-THC (41): Pentobarbital, phenobarbital, SKF 525-A, amphetamine and meprobamate all inhibited delta-9-THC metabolism in vitro; under similar conditions morphine and mescaline had no effect. In contrast to these general findings, only SKF 525-A affected delta-9-THC metabolism in vivo. It appears, therefore, that the in vivo interactions between delta-9-THC and other centrally acting drugs cannot be explained by an alteration in delta-9-THC metbolism.

Recent examinations of the delta-9-THC biotransformation products of rabbit and dog liver microsomes have revealed the presence of 1,2-epoxyhexahydrocannabinod (3, 55); and a comparison of metabolites from the perfused dog lung and from dog hepatic microsomes has led to the discovery of side-chain hydroxylated derivatives (55). Moreover, there is now evidence that CBN and its oxidized derivatives are normal metabolites of delta-9-THC. CBN has been identified in human plasma following marihuana smoking (27), in rat bile (54) and in rat blood (28) after intravenous injection of delta-9-THC. Oxidized metabolites of CBN have also been identified (2, 5); and a new metabolite containing two carboxyl groups has been isolated from rabbit urine (30). Both rat and rabbit liver microsomes were found to convert CBN into a number of side-chain hydroxylated compounds

(53). In addition, marihuana metabolites in human urine have been extracted by a new method which separates them into neutral, weak and strong acid fractions (17).

Various aspects of the distribution of the cannabinoids in the body have been investigated: Thus, one research group has found that the properties of delta-9-THC in plasma are a function of the method of administering the drug (10). In this study, delta-9-THC was administered either intravenously in polyethylene glycol or in rat serum, or in the form of cannabis smoke. Plasma disappearance curves varied, depending upon the method of administration, and, compared with the other two means of administration, injection in serum resulted in a slower elimination from plasma, a lower proportion of metabolites relative to delta-9-THC and a different distribution of binding to plasma proteins.

Other investigators found that the plasma-protein distribution of delta-9-THC after intravenous administration differs in female and male rats (7); and at all doses tested, the response in females was more pronounced. The latter finding correlated with that of higher tissue concentrations of delta-9-THC and its metabolites in the female; therefore, the enhanced activity of delta-9-THC in the female rat may be due to the higher tissue cannabinoid concentrations in the brain.

The relationship between tissue-drug concentration and pharmacological activity was extended in a comparative study of the effects of delta-9-THC and dimethylheptopyran (DMHP) on mouse immobility (21). Like delta-9-THC, the brain concentrations of DMHP and its hydroxylated metabolite correlated with the behavioral effect (21). Despite DMHP's greater potency, the fraction of the dose in the brain was smaller than that of delta-9-THC; thus, the potency difference between delta-9-THC and DMHP appears to be a consequence of the latter's greater activity at the site of action.

Plasma concentrations of delta-9-THC, 11-hydroxy-delta-9-THC, CBN and CBD were measured by radiommunoassay as a function of time after their intravenous administration in the rabbit (45). Delta-9-THC was unlike the other drugs, because plasma values for reacting substances rose for several minutes after injection, presumably due to the rapid formation and re-entry of the 11-hydroxy metabolite into the plasma. In humans, this metabolite leaves the plasma more rapidly than does delta-9-THC (33); an observation that has been confirmed in mice (32).

In a study of lactating ewes, both delta-9-THC and its metabolites were recovered from the milk for as long as 96 hours after administration of a single, intravenous low dose (15). Other investigations have shown that biliary excretion in rats accounts for the elimination of 60% of an intravenous dose of delta-9-THC (3mg/kg) (40), that biliary excretion remains unchanged when tolerance to THC develops (39), and, finally, that most of the metabolites in the bile are highly polar substances.

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CHAPTER 3

Toxicological and Pharmacological Effects

The toxicological research reviewed in the present Marihuana and Health report is the result of the continuing need to identify and evaluate the toxicological properties of marihuana. To fill this need, a series of inhalation toxicity studies have made two major contributions. First, in the absence of detailed pathological studies in humans, marihuana has been administered to numerous species in a wide range of dosages by a variety of routes—including inhalation. The report that chronic administration of low doses by smoke inhalation results in a toxicity comparable to that elicited by other routes of administration serves to validate the conventional animal toxicity studies which are based on either the oral or parenteral route. Accordingly, the mass of animal data collected in the past few years leads to the conclusion that, to date, regardless of the route of administration, the observed toxicity of marihuana is not associated with any serious pathological changes.

Secondly, until the inhalation studies, most cannabinoid toxicity research was restricted to the principal psychoactive constituent of cannabis, delta-9-THC: now, however, cannabidiol and cannabichromene—both formerly considered pharmacologically inactive—are known to contribute significantly to the toxicity and lethality of marihuana. Clearly, future toxicological evaluations of cannabis constituents must be extended to all the major, naturally occurring cannabinoids, both alone and in various combinations.

Another important aspect of toxicological research arises from the reported effects of marihuana on such cellular components and products as lipids, proteins, nucleic acids, hormones and neurochemical transmitters. An association between some of these effects and animal behavior has now been made; most, but not all, of the changes appear to be readily reversible. These cellular effects and their implications are not easily understood, but they may reflect subtle alterations in function independent of any gross pathological changes. With chronic drug exposure, however, these subtle changes may evolve into significant toxicological factors.

The study of the pharmacological properties of marihuana is important for at least three reasons: (1) to define its effects, particularly its possible toxic effects: (2) to determine the potential interaction of its effects with various pathological states (e.g., coronary artery disease, liver disease, epilepsy); and (3) to evaluate the potential therapeutic uses of the cannabinoids. During the past year there have been significant contributions to the attainment of all these objectives. Several studies have recognized the ability of the cannabinoids to interact, not only with one another, but more importantly, with other

drugs; the interaction in some instances results in the enhancement of a drug effect, in others in an antagonism. Such a complex set of effects has been described in the case of the barbiturates, the amphetamines and alcohol. The signficance of this interaction potential is obviously not limited to drugs used only for illicit purposes: From the reported interaction effects, the concurrent use of marihuana with licit drugs could conceivably result in an increased toxicity, a diminished therapeutic effectiveness or, even, an enhanced therapeutic effectiveness.

Another report of a potentially significant drug interaction centers on the delta-9-THC blockade of the morphine-abstinence syndrome. If this effect is confirmed, then the characteristics and consequences of the interaction should be defined further, particularly with reference to other drugs known to block the opiate-abstinence syndrome.

The pharmacological studies included in the present Marihuana and Health report reveal the toxic influence of marihuana on preexisting pathological states (62): Thus, the clinical description of the adverse effect of smoking marihuana on cardiac function in patients with coronary artery disease is a significant contribution toward a more comprehensive picture of the toxicity of cannabis. There are also reports of animal data indicating that the use of marihuana may adversely affect the control of seizures. This interpretation is based on several observations of marihuana's central-nervous-system excitatory properties and on the hyperexcitability following withdrawal from repeated delta-9-THC treatment. These potentially unfavorable interactions with epilepsy may be independent of the anticonvulsant properties of marihuana, as is the case with some antiepileptic drugs, such as phenobarbital.

The Report (62) contains descriptions of two pharmacological effects that have definite clinical potential: The decrease in intraocular pressure and the anticonvulsant activity, both of which are described in sufficient detail to warrant serious consideration of their therapeutic application. Furthermore, the quantitative evaluation of the relative anticonvulsant and neurotoxic activity of several cannabinoids has demonstrated that a potentially useful therapeutic effect of cannabidiol is at least partially separable from the motor toxicity of marihuana, a finding which is further supported by the report of cannabidiol's complete lack of psychotoxicity in humans. A comparable pharmacological selectivity for other cannabinoid effects deemed potentially valuable clinically is thus a distinct possibility. Finally, the introduction of numerous synthetic cannabinoids presents an opportunity to search for the most appropriate agent for any given desired effect.

TOXICOLOGICAL EFFECTS

Investigators have continued to evaluate the toxicity associated with chronic exposure to the cannabinoids using various routes of administration and several different species. Experiments have been of two basic types: those designed to study lethal effects produced by the chronic administration of massive doses, and others designed to study sublethal toxicity produced by relatively low doses, such as those commonly used by humans. The chronic low-dose work now includes rat studies of toxicity following smoke inhalation (71): The daily doses given to 1-, 5- and 23-day exposed animals were analogous to

those taken by humans, and the results indicate that inhalation of delta-9-tetrahydrocannabinol (delta-9-THC) can produce the characteristic marihuana central-nervous-system (CNS) toxic effects (depression and excitation) elicited by other routes of administration. These effects, like those associated with other routes of administration, appeared in the absence of any pathological changes, and tolerance ultimately developed to most of them. In a study of the inhalation toxicity of Turkish marihuana (high in cannabidiol and cannabichromene and low in delta-9-THC content) rats were daily exposed to smoke 5 days per week for 25 days (72). This treatment resulted in various manifestations of CNS depression and in a dose-related lethal effect—respiratory arrest; such results demonstrate that cannabidiol (CBD) and cannabichromene (CBC) can contribute to the toxicity of marihuana.

Massive oral doses of delta-9-THC or crude marihuana extract administered to rats daily for 28 to 91 days have been used to determine toxic neurochemical effects (59): After 28 days of treatment, significant decreases were observed in total brain protein, ribonucleic acid (RNA) and acetylcholinesterase activity. These neurochemical changes in rats coincided with the appearance of the CNS stimulation (fighting behavior and convulsions) characteristic of chronic marihuana treatment, and, like neurotoxicity, were partially reversed by 91 days of continued administration.

In a study similar to that described immediately above, neurochemical changes were evaluated in rats treated for as long as 180 days; in this instance, however, the doses were relatively low—2, 10 or 50 mg/kg/day orally (60). The two lower doses of delta-9-THC were again analogous to the drug content of the marihuana and hashish consumed by humans. (This work is the counterpart of a low-dose, chronic-toxicity study (74) referred to in the 1974 Marihuana and Health report (62). Neurochemical analyses of four areas of the brain (frontal cortex, parietal cortex, subcortical regions and cerebellum) were made at various times after the initiation of chronic treatment and generally showed neurochemical changes comparable to those produced in the massive-dose study described above. In the lower-dose study, however, changes required longer periods of treatment to appear and varied in the different areas of the brain. Some of the behavioral and neurochemical changes were sex-linked, and several occurred after the development of tolerance to the behavioral effects. Furthermore, a few of the neurochemical alterations were reversible, even after a 30-day recovery period.

Neurotoxicity and EEG, effects of chronic oral treatment of rats and rhesus monkeys have also been described (79, 80). In rats acute treatment with 10 mg/kg delta-9-THC increased the frequency of surgically induced polyspike activity, while chronic treatment resulted in subcortical spike bursts with concomitant seizures. In the rhesus monkey chronically treated with crude marihuana extract equivalent to 12.5 mg/kg delta-9-THC or more, the neurotoxic manifestations always preceded and outlasted the effects on the EEG, and tolerance developed more rapidly to the EEG effects than to the neurotoxicity. The results suggest that the neurotoxic effects become manifest at lower doses than the characteristic EEG effects, findings similar to those previously reported in humans.

Monkeys treated intravenously (i.v.) with delta-9-THC exhibited, at the injection site, such toxic reactions as edema, necrosis, ulceration and fibrosis (83). In order to elaborate the local toxicity findings, the drug was chronically administered subcutaneously (s.c.) to rabbits in doses ranging from 15.9 to 153.4 mg/kg/day. The dermal responses, which were generally dose-related, included erythema, edema, ulceration and nodule formation. These results illustrate that the use of marihuana i.v. may be accompanied by local toxic reactions. The chronically treated animals displayed dose-related decreases in body and liver weights, in glycogen content of the liver, and in blood sugar and alkaline phosphatase activity; serum potassium concentration was elevated. As in other chronic toxicity studies from this group, no pathological tissue effects—other than those at the injection site—were discernible.

A study of the influence of different routes of administration and vehicles on the lethal dose 50 (LD50) values of delta-9-THC has also been made (73). The oral LD50 for delta-9-THC in an aqueous emulsion of sesame oil and polysorbate 80 was similar to that obtained with a pure sesame-oil vehicle, indicating that the composition of the emulsion did not affect the LD50. Furthermore, the i.v. LD50 for the same aqueous formulation was essentially identical to the inhalation LD50. In general, the results established the validity of the i.v. route of administration in the investigation of the pharmacology and toxicology of marihuana-like substances.

The continuing interest in the carcinogenic potential of marihuana smoke has brought forth a report that marihuana tar painted on mouse skin produced a variety of effects on squamous cells, including metaplasia of sebaceous glands (20). This good correlation with the established carcinogenicity of tobacco smoke led the investigators to conclude that cannabis smoke will also be carcinogenic, a conclusion which is supported by bioassays of marihuana tar on mouse skin. Both tumorgenicity and tumor-promoting activity were revealed although at levels significantly lower than those resulting from tobacco smoke (41). This contrasts with in vitro observations on human lung explants which suggest that cannabis smoke may be more carcinogenic than tobacco smoke (91).

In another investigation, marihuana smoke produced a dose-dependent depression of the bactericidal activity of pulmonary alveolar macrophages: the effect was related to a water-soluble constituent in the smoke rather than to delta-9-THC (23). It is possible that the toxicity of marihuana smoke to the alveolar macrophage may impair the ability of this cell to function in the host-defense mechanism of the lung.

Numerous reports have appeared describing the effects of delta–9–THC on the endocrines. The main thrust of research in this area has aimed at pituitary and gonadal hormones. (See Appendix G "Human Effects" for a detailed review of the latter.) One of the previously reported effects of heavy marihuana use in humans was gynecomastia (37). This effect has now been produced in rats given 1 mg/kg delta–9–THC s.c. for two to three weeks (38). In a related study, delta–9–THC in male rates increased pituitary weight, total pituitary prolactin and the concentration of prolactin in serum (24), but in a similar

study, delta–9–THC decreased, rather than increased, serum prolactin concentrations (57). The discrepancy in these results may be due in part to differences in dosage: The effect in the former study was obtained at 16 mg/kg. In humans, marihuana use has had no apparent effect on serum prolactin. The gynecomastia described above was associated with normal serum hormone values, while another group of chronic marihuana users was also normal (56).

Research into the effect of delta–9–THC on other pituitary hormones has indicated that in rats delta–9–THC in doses of 5 to 20 mg/kg inhibited growth hormone and stimulated adrenocorticotropic hormone secretion; daily administration of 20 mg/kg for 20 days did not produce tolerance to these effects (55). The findings suggest that delta–9–THC acts as a stress stimulus of the hypothalamicpituitary axis. A similar response to delta–9–THC in the mouse was evidenced by an increase in corticosterone concentration in plasma (69), although tolerance to the effect on steroid secretion rapidly developed in this species. The work of one group of investigators has shown an inverse relationship between plasma corticosterone and the amount of 5-hydroxytryptamine in whole brain. A positive correlation between the steroid value and aggressive behavior in ovariectomized rats following chronic cannabis treatment was found (66). Aggressiveness was abolished by estrogen treatment, suggesting that previously described sex differences in response to cannabis may, in part, have been due to female variability during different phases of the estrus cycle.

The inhibitory effect of delta–9–THC on the secretion of growth hormone also manifested itself in prepuberal male rats (17), but in adult female rats high doses of the drug (50 mg/kg) elevated serum growth hormone values (28). In a study of male mice chronically treated with delta–9–THC, growth was depressed in a way similar to that seen in estradiol treated animals, suggesting that delta–9–THC can exert an estrogen-like effect (78).

PHARMACOLOGICAL EFFECTS

The similarities in psychological actions between the liqueur absinthe and cannabis have led to a molecular structural comparison of their active principles, thujone and tetrahydrocannabinol (26). Because the substances have a similar molecular geometry and similar functional groups, they may exert their psychic effects by interacting with a common receptor in the CNS. The receptor should have a binding site for oxygen, a planar region for the allyl group and pockets, or cavities, for fitting with alkyl and hydrogen groups that are common to both drugs. The importance of the phenolic hydroxyl group in tetrahydrocannabinols in eliciting delta–9–THC-like activity in animals has also been established (86).

Studies of the effects of delta–9–THC on sleep-wakefulness patterns referred to in the 1974 Marihuana and Health report (62) have been expanded to include the male squirrel monkey whose patterns are similar to those of the human (1). Chronic treatment reduced slow-wave sleep time, which failed to return to normal, even after a 30-day recovery period. In addition to this change in sleep pattern, the time

spent in Stage 1, or drowsy sleep was increased in treated animals and this change also persisted throughout the recovery period.

The analgesic activity of delta–9–THC has now been described in the dog, as well as in the rat, mouse and rabbit (54). Tolerance, which has been found to develop to such other effects in the dog as ataxia and sedation, also developed to the analgesic effect. Two cannabinoid-free extracts (an aqueous extract and a volatile oil) of marihuana also were found to elicit analgesia in mice. The analgesic potency of the extracts was much lower than that of delta–9–THC, but the nature of the analgesic material and its interaction with delta–9–THC are still unknown.

Many cannabinoids, in addition to delta-9- and delta-8-THC, are known to be anticonvulsants: These include cannabinol (CBN), dimethylheptylpyran (DMHP) and some of its isomers; 11-hydroxy-delta-9-THC (46); 8-alpha, 11-dihydroxy-delta-9-THC (45); and some new benzopyrans (70). Moreover, the activity of CBD has been confirmed and the compound subjected to a variety of seizure tests which have demonstrated that in its anticonvulsant properties the drug more closely resembles diphenylhydantoin (DPH) than does delta-9-THC (44, 49, 85). The interaction of CBD with other anticonvulsant drugs has also been described in studies that generally show that, in a maximal electroshock test in mice, CBD clearly enhances the potency of delta-9-THC, DPH and phenobarbital (PB). The determination of the protective indices (toxic dose/anticonvulsant dose) of several cannabinoids in mice indicates that motor toxicity is a separable effect from anticonvulsant activity (46); for example, compared with delta-9-THC, DMHP is relatively more toxic and CBD significantly less toxic. Furthermore, the separation of toxicity from anticonvulsant activity is dramatically illustrated by the report that massive i.v. doses of CBD in humans do not produce either the marihuana-like psychotoxicity or tachycardia (68).

In rats and mice subjected to a maximal electroshock test, tolerance to the protective effect of delta-9-THC and CBD rapidly developed (46, 47), but a similar response to repeated treatment was associated with DPH and PB (47); in addition, tolerance to delta-9-THC or CBD involved cross-tolerance to DPH and PB (47). Tolerance has also been described for the antiseizure activity of delta-9-THC in the gerbil, but in this case it did not develop to the neurotoxic effects (82). It should be noted, however, that a study of the influence of repeated daily drug treatment on the results of several anticonvulsant tests indicates that tolerance does not develop to all the anticonvulsant properties of the cannabinoids (48). In fact, in some tests anticonvulsant activity increased, rather than decreased, with repeated treatment. Similar results were obtained with DPH but not with PB. The evidence suggests that the tolerance observed is not a dispositional but a functional adaptation. For example, in one study tolerance to protection against a maximal electroshock developed concurrent with an accumulation of cannabinoids in the CNS and increased sensitivity to cannabinoids in certain anticonvulsant tests, while no change occurred in plasma delta-9-THC concentration or in barbiturate sleep time (48).

Previous reports mentioned descriptions of some excitatory properties of delta-9-THC, especially in conjunction with toxicity produced

by chronic, high-dose treatment. Withdrawal from repeated treatment with anticonvulsant doses of delta-9-THC also resulted in CNS hyperexcitability, as measured by a decrease in the 6-Hz-electroshock threshold test for minimal seizures (49, 50); no such withdrawal increase manifested itself in the case of CBD or DPH. On the other hand, withdrawal hyperexcitability to delta-9-THC could not be demonstrated when pentylenetetrazol (PTZ) was used to elicit minimal seizures (11). Following low-dose, i.v. administration, convulsant effects of delta-9-THC have been observed in a special strain of rabbits (19). Furthermore, delta-9-THC administered i.v. to the photosensitive baboon *Papio papio* resulted in an epileptiform EEG response, 3/sec rhythmic spikes and waves (63); no doses were anticonvulsant against the photically elicited myoclonic activity, but high doses (1–5 mg/kg) enhanced seizure responses in some cases.

In the area of cannabinoid hypothermic activity, one recent study compared several cannabinoid preparations with chlorpromazine in mice (58) and ranked them in order of decreasing potency as follows: chlorpromazine, marihuana extract, distillate, DMHP, delta-8- and delta-9-THC. Tolerance to the effects of both delta-9-THC and chlorpromazine rapidly developed, although more rapidly to the former drug. Antipyretic activity for delta-9-THC, suggested by previous reports, have now been confirmed in mice (16). Additionally, with respect to the mechanism which lowers body temperature, the results from direct and indirect calorimetry measurements suggest that delta-9-THC-induced hypothermia is associated with both a decrease in heat production and an increase in heat loss (4, 88). In brain, some investigators have found a decreased tissue metabolic rate following in vivo drug administration and a subsequent tolerance (64). Such an effect on metabolic rate could be mediated by either a direct or indirect action of the cannabinoids: A direct effect of several cannabinoids on tissue oxygen consumption in vitro has been described by another research group (14) who reported that the cannabinoids depress the oxygen consumption of homogenates of liver, heart, brain and skeletal muscle. Moreover, mitochondrial preparations from the latter two tissues were studied further and their metabolic rates were also depressed. The dose-response data from the oxygen consumption research indicate that hypothermic doses of delta-9-THC yield tissue-drug concentrations sufficient to depress metabolic rate directly.

Recent research into the cardiovascular effects of marihuana has yielded a number of studies on various facets of this subject (cf. 15). For example, it has been found that in rats tolerance does not develop to the bradycardia commonly associated with chronic marihuana treatment (53). In addition, the effect of delta-9-THC on cardiac function has been described in pentobarbital-anesthetized dogs with an electrically maintained constant heart rate (9). In this study, the drug decreased aortic blood pressure, cardiac output, left ventricular peak pressure and left ventricular end-diastolic pressure, but the contractility index was not affected. The decrease in cardiac output could be restored to normal by elevating left ventricular end-diastolic pressure with an expansion of plasma volume. In dogs with a maintained constant cardiac output, delta-9-THC decreased blood pressure and total peripheral resistance, but increased intravascular blood volume. These

results indicate that the delta-9-THC induced decrease in cardiac output in the presence of constant cardiac rate is due to a decreased venous return, rather than to a decrease in myocardial function.

In a study using spinal preparations, delta-9-THC exerted no cardiovascular effects; hence, the role of the CNS in mediating delta-9-THC's effects on heart rate and blood pressure was investigated in cats anesthetized with chloralose (87). Spinal transection (C1–C2) abolished the drug-induced bradycardia and hypotension. The delta-9-THC-caused bradycardia was also blocked by the surgical removal of tone to the heart, but neither heart-rate nor blood-pressure effects were modified by bilateral vagotomy. Sympathetic outflow in the inferior cardiac nerve decreased after delta-9-THC administration although peripheral sympathetic functions were unaffected; thus, the cardiovascular effects of delta-9-THC appear to be due to a CNS action which results in a decrease in sympathetic tone.

Other investigators have examined the relationship between the sympathetic nervous system and delta-9-THC's cardiac effects in terms of changes in the uptake of noradrenaline by the heart and have found that delta-9-THC, like cocaine, can decrease in a dose-related manner the uptake of noradrenaline by the isolated, perfused rat heart, although cocaine appears to be about ten times more potent than delta-9-THC (32). The significance of such effects is not yet clear, but of great interest is the report that smoking marihuana can adversely affect cardiac function in patients with angina pectoris (3). In these patients, smoking one marihuana cigarette containing 19.8 mg delta-9-THC decreased exercise performance significantly more than smoking one placebo cigarette.

The cannabinoids' ability to decrease intraocular pressure is still inciting investigation and several congeners of delta-9-THC, administered either systemically or topically, have now been tested. These are listed in order of decreasing efficacy: 11-hydroxy-delta-9-THC; delta-9-THC; 8 alpha, 11-dihydroxy-delta-9-THC; SP111A; other derivatives (33). Delta-9-THC can decrease the pressure in the rabbit eye by 25% and increase outflow capacity by 70% and the role of the sympathetic nervous system in mediating these effects has been established (34, 35, 36). The alpha-response is an enhanced total outflow facility and the beta-response is a vasodilatation of the efferent vessels from the anterior uvea, thereby causing a decrease in the formation of aqueous humor. Part of delta-9-THC's effect on intraocular pressure appears to be mediated through these actions on sympathetic receptors; but most arises from a central effect.

The influence of cannabinoids on biogenic amines continues to be a focal point for studies of their mechanism of action. In a rat study of repeated delta-9-THC treatment on brain metabolism of 5-hydroxytryptamine (5-HT) and norepinephrine (NE), the products of metabolism were isolated from whole brain following the intracisternal administration of radiolabelled 5-HT or NE (40). Chronic treatment yielded a decrease in the metabolism of 5-HT but an increase in that of NE. In another study in the rat, the effect of hypothermic doses of delta-9-THC on the metabolism of 5-HT and NE in the hypothalamus and brainstem was reported (89), and these results show that there are no changes in either the amount or the turnover of these amines in the

two parts of the brain investigated. Several cannabinoids have been examined for their effect on the uptake of NE, 5-HT, dopamine (DA) and gamma-aminobutyric acid (GABA) by synaptosomes derived from various regions of the rat brain (6). The findings indicate that cannabinoids can inhibit the uptake of NE, 5-HT and GABA by hypothalamic synaptosomes; in addition, a discussion of the structural requirement for these effects is included. Delta-9-THC can also augment the release of NE from the isolated rat vas deferens (32), an observation which has led to the suggestion that the release of transmitter from peripheral stores may, in part, account for the hypotensive activity of delta-9-THC. Delta-9-THC can decrease the uptake of DA by crude striatal synaptosomal preparations (42); however, amphetamine is more potent in this regard. Delta-9-THC also appears to alter the intraneuronal disposition of DA without any effect on its metabolism (65). It is possible that these effects are related to delta-9-THC's known interaction with amphetamine.

Studies of the mechanism of action of delta-9-THC have been expanded to include its effect on cyclic adenosine, 3′,5′-monophosphate (cyclic AMP), and investigators have found that low doses of delta-9-THC (0.1–1.0 mg/kg intraperitoneally) cause a 50–160% increase in brain cyclic AMP, whereas higher doses (2.0–10 mg/kg) depress cyclic AMP 30–60% (27). This biphasic response apparently correlates with other previously reported biphasic responses in biogenic amines, temperature regulation and behavior.

The influence of tetrahydrocannabinols on brain acetylcholine content has also been investigated (5). The intravenous administration of 5 mg/kg delta-9- or delta-8-THC was found to decrease brain acetylcholine content, while 11-hydroxy-delta-9-THC, a metabolite, was ineffective. Delta-8-THC did not appreciably alter either acetylcholinesterase or choline acetyltransferase. The decrease in acetylcholine was not observed in rats treated with 6 mg/kg intraperitoneally (90). In contrast to the results described above for acute experiments, chronic oral cannabinoid treatment produced a decrease in brain acetylcholinesterase activity, as well as a decrease in total protein and RNA (59); however, no changes were observed in brain lipid, glycolipid or cholesterol concentration. In the chronic study, the neurochemical changes coincided with the onset of neurotoxicity; furthermore, both were partially reversed during continued drug treatment. The mechanism of some of the anticholinergic effects of the cannabinoids remains to be elucidated.

The relationships between cannabis and prostaglandins have been studied further and it has been confirmed that cannabinoids inhibit the formation of prostaglandins PGE1 and PGE2 but they also stimulate PGF production (22). In another study, eugenol, a minor volatile constituent of cannabis, was found to be a more active inhibitor of PGE1 synthesis than was delta-9-THC. This observation, combined with a demonstration of pharmacological activity in the essential oil fraction (76), indicates a need to consider the role of these substances in the pharmacology of cannabis. The release of PG-like substances by delta-9-THC from both rabbit kidney and guinea-pig lung has been reported (52): These substances produced renal vasodilation and pulmonary vasoconstriction, responses which were blocked

by aspirin. The former effect may account for the diuretic property ascribed to delta-9-THC, while the delta-9-THC-caused release of PG-like material may be related to the increase in PG synthesis referred to above (22).

An examination of the influence of acute and chronic delta-9-THC treatment on the lipids of rat brain subcellular fractions has revealed the following effects: Acutely, the lipid content of the mitochondrial, synaptosomal and myelin fractions decreased, but in the microsomal fraction all major lipid components increased; chronically, these changes tended to return to normal (75). Other reports have noted a lysis of rat liver lysosomes in vitro by high concentrations of delta-9-THC (8), and the uptake of delta-9-THC in vivo by the lysosomes (43).

Numerous interaction studies of marihuana constituents have been undertaken since the last report and the interaction between cannabinoids, particularly between delta-9-THC and CBD, has received a great deal of attention. CBD's ability to antagonize some of the behavioral effects of delta-9-THC has been established and studies have been extended to the investigation of other effects. In one such study, prior treatment with CBD blocked the delta-9-THC induced catatonia, corneal areflexia and aggresiveness in REM sleep-deprived rats (51). In addition, CBD potentiated the delta-9-THC analgesic effect and impairment of rope climbing. In another study, pretreatment with apparently inactive doses of CBD reduced the depressant effects of delta-9-THC on body temperature, on heart rate and on respiration (7). CBD also reduced the depressant effects of delta-9-THC on variable-interval and fixed-interval schedules of food reinforced operant behavior (25). In these tests, high doses of CBD did affect these behavioral parameters, suggesting that CBD can function as a partial agonist. A comparison of the interaction of CBD and CBN with delta-9-THC showed that CBD intensified delta-9-THC's effects on animal motility, on food and water intake, on body temperature, on catalepsy, and on hexobarbital sleep time (30). CBN, in general did not alter the activity of delta-9-THC, except in the barbiturate sleep-time test. In this case, CBN, in contrast to CBD, blocked the delta-9-THC prolongation of hexobarbital sleep time, thus corroborating an earlier report of CBN antagonism. The evidence presented suggests that CBD heightens the effects of delta-9-THC by a metabolic interaction at the level of the hepatic drug-metabolizing enzymes; on the other hand, the observed antagonism between CBN and delta-9-THC on sleep time appears to be a central interaction (29). The ability of CBD to potentiate the anticonvulsant activity of delta-9-THC was described above (85). An in vitro potentiation has also been reported (2). Both delta-9-THC and CBD were found to depress intestinal motility, but delta-9-THC was more potent. Inactive doses of CBD increased the depressant effect of delta-9-THC, demonstrating that potentiation was not necessarily mediated by a CBD blockade of delta-9-THC's metabolism.

The interaction of CBN with depressant, excitatory and peripheral effects of delta-9-THC has also been described (81) : Inactive doses of CBN appeared to enhance the depressant effects and slightly inhibit excitatory effects, while having no effect on a peripheral response to delta-9-THC.

Additional studies have focused primarily on the interaction of cannabinoids with other drugs. Acutely, delta-8-THC, in a dose-related manner, prolonged alcohol sleep time, but tolerance developed to this interaction with repeated cannabinoid exposure (31). The enhanced sleep time produced acutely cannot be attributed to an altered rate of alcohol metabolism (31). The possibility that some of the effects of delta-9-THC are mediated by an action on chemical transmitters has been pursued by measuring the cannabinoid's influence on the LD50s of certain drugs. It was found to intensify the toxicity of some cholinergic drugs but to attenuate the toxicity of others; the toxicity of adrenergic drugs was significantly reduced by the pretreatment with delta-9-THC and, finally, delta-9-THC increased the toxicity of a 5-HT-blocking drug (77).

The interaction studies of cannabinoids and barbiturates have been expanded to include ether anesthesia (13, 61). Cannabis extract prolonged the duration of both barbiturate and ether anesthesia. However, after repeated treatment, tolerance developed to the interaction with ether but not to that with pentobarbital. CBN also prolonged the duration of ether anesthesia, but CBD tended to antagonize ether. The investigators suggested that the failure of others to observe any such effect on ether anesthesia may have been the consequence of the variable cannabinoid composition of cannabis extracts.

A study of the interaction of delta-9-THC pretreatment with d-amphetamine in aggregated mice, indicated that cannabinoid pretreatment can potentiate motor activity and lethality without affecting hyperthermia (21): these effects were associated with a decrease in the amount of amphetamine in the brain. The influence of a combined treatment of detla-9-THC and methamphetamine on the EEG and on behavior has been described by other investigators who reported methamphetamine reversed the delta-9-THC effects o nthe EEG, but the combination of drugs produced some striking behavioral disturbances, which appeared to be a potentiation of methamphetamine toxicity (18). An interaction between delta-9-THC and a naloxone-precipitated abstinence in morphine-dependent rats appears to exist for a single delta-9-THC pretreatment can block in a dose-related manner the naloxone-induced abstinence signs. Pretreatment with 10 mg/kg CBD failed to produce any such effect (39).

It should be noted that two comprehensive reviews (67, 84) on the general subject of the pharmacology of marihuana have appeared since the 1974 Marihuana and Health report (62).

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CHAPTER 4

Preclinical Effects: Unlearned Behavior

As the studies reviewed in the four previous Marihuana and Health reports (44, 45, 46, 47) have shown, the cannabinoids produce a variety of effects on unlearned behavior in different animal species. The literature pertaining to cannabis and unlearned behavior is now quite voluminous. Consequently, this appendix focuses primarily on the relevant literature which has appeared since the last report, although some attempt is made to consider this literature in light of previous findings. Furthermore, for the sake of exposition the appendix is organized around four categories of unlearned behavior: gross behavior; activity and exploration; consummatory behavior; and aggressive behavior.

GROSS BEHAVIOR

Much of the early preclinical research with canabinoids investigated the effects of these drugs on the gross behavior of a wide range of animal species. As has been discussed in previous Marihuana and Health reports and recent reviews of the animal literature (e.g., 53) a variety of gross behavioral changes are induced in animals by the cannabinoids. Included among these effects are; catalepsy, ataxia, abnormal body postures, hypersensitivity, and hyperactivity. Subsequent to this earlier work on gross behavioral changes, much of the preclinical work with cannabinoids pertained to learned rather than unlearned behavior. Most recently, however, there has been a renewal of interest in the gross behavioral changes induced in animals by cannabinoids. The primary reason for this has been the recognition that complex pharmacological interactions may occur among the cannabinoids.

The majority of cannabinoids research on unlearned behavior has used delta-9-THC or delta-8-THC since these particular cannabinoids have been established as the major active components of cannabis samples (49). However, several researchers reported that the pharmacological activity of cannabis samples was not always entirely explained by the tetrahydrocannabinol content of the samples (7, 36, 55). This led to the suggestion that interactions between THC and other cannabinoid constituents of cannabis, namely cannabidiol (CBD) and cannabinol (CBN), may be important. This suggestion was supported by findings that CBD inhibits the metabolism of delta-9-THC (25, 35, 42).

Experiments dealing with interactions of cannabinoids on gross unlearned behavior are still few in number. However, those interactions which have been observed appear, at this time, to be complex and are not always consistent among experiments. For example, in

testing the effects of cannabinoids on catalepsy in rodents, investigators have found CBD and CBN administered alone to be either active (37, 61) or inactive (24). Moreover, when administered in combination with delta-9-THC, CBN has been reported either to have no effect on catalepsy (24) or to potentiate delta-9-THC induced catalepsy (61). Finally, CBD in combination with delta-9-THC has been reported to prolong (24) or to enhance (37) catalepsy induced by delta-9-THC.

The interactions between the cannabinoids on drug-induced loss of the righting reflex (anesthesia, sleeping-time) seem to be particularly complex (14, 15, 25, 37, 41, 43, 61). For example, CBN antagonizes delta-9-THC effects on pentobarbitone- (41) and hexobarbitone- (25) induced loss of the righting reflex but potentiates delta-9-THC-ether effects on the same unlearned response system in the same animal species (43). The complexity of these and other interactions (14) will most likely be better understood with additional research—especially research which can distinguish between drug interactions involving CNS activity and those involving cannabinoid-induced changes in tetrahydrocannabinol metabolism.

As would be expected, THC interacts with drugs other than the cannabinoids to affect unlearned gross behavior. Recent experiments have shown that delta-8-THC potentiates the loss of righting reflex induced in rats by alcohol (27) while delta-9-THC potentiates some, and antagonizes other, amphetamine-induced postural and activity behaviors in rats (30) and rabbits (16).

ACTIVITY AND EXPLORATION

Based on the research available at the time, the 1974 Marihuana and Health report (47) concluded that "cannabinoids generally suppress the spontaneous motor activity and exploration of animals, although findings regarding these effects are limited, as always, by drug route, time-effect, and drug-response considerations" (20, 26). The suppression effect of delta-9-THC on spontaneous motor activity has been confirmed by two recent studies (6, 56). In one of these (6), oral doses of delta-9-THC ranging from 1.25 mg/kg to 40.0 mg/kg were administered acutely to mice. The lowest drug dose produced a significant increase in activity while the remaining drug doses produced a dose-dependent suppression of activity. Other mice were used to investigate tolerance to the suppressive effects of 40.0 mg/kg of delta-9-THC (p.o.) on spontaneous activity. Complete tolerance developed after one dose and had a duration of less than four days.

Another aspect of this latter study (6) deserves mention. Specifically, the activity of mice that had been previously habituated to the experimental apparatus was not suppressed by a 40.0 mg/kg dose of delta-9-THC. This finding is in accord with other research (17, 19) which shows that prior habituation to an experimental situation can alter the effects of THC on motor activity in animals.

Delta-9-THC doses of 30.0, 60.0 and 120.0 mg/kg were administered subcutaneously to pregnant rats on the fourth day of gestation (66). It was found that delta-9-THC produced an increase in abnormal pregnancies but that it had no significant effect on the locomotor activ-

ity of the offspring. This latter finding is at odds with a previous experiment (7) in which effects were observed on the unlearned behavior of offspring from pregnant rats that had been administered delta-9-THC subcutaneously during the tenth to twelfth days of gestation. Additional research is needed to determine whether delta-9-THC has a direct action on the developing fetus which becomes manifest in the unlearned behavior of offspring.

The spontaneous activity of rats was additionally used to study the drug interaction between delta-9-THC and phencyclidine (56). It was found that an increase in activity produced by 5.0 mg/kg intraperitoneal injections of phencyclidine was antagonized by oral doses of delta-9-THC, ranging from 2.5 to 10.0 mg/kg, in a dose-related manner.

Exploratory behavior and performance on simple unlearned motor tasks have also been used recently to study the interactions of delta-9-THC with other cannabinoids. First of all, it has now been reported that CBD and cannabichromene (CBC), in inhaled doses from 1.0 to 2.0 mg/kg decreases exploratory behavior of rats in a dose-related manner (57) while CBN (10.0 mg/kg; i.p. injection) significantly increased exploration-ambulation in rats (61). However, CBD did not affect the motor coordination of mice over a wide range of i.p. doses (62). In combination with delta-9-THC, both CBD (37) and CBN (61) produce a pharmacological interaction on exploratory behavior in rats, although delta-9-THC and CBD do not seem to interact to affect motor coordination in mice (62).

CONSUMER BEHAVIOR

Prior to 1973 delta-8-THC, delta-9-THC, hashish resin, and pyrahexyl were all shown to produce reductions in food and water intake, with a consequent weight loss, in animals. Research appearing since that time, much of which was reviewed in the fourth Marihuana and Health (47) report, has generally confirmed and extended these findings for delta-8-THC and delta-9-THC (3, 28, 32, 33, 39, 59, 60). In addition, inhaled doses of CBD and CBC have been recently shown to reduce the rate of growth in rats and to decrease their food and water consumption in a dose-related manner (57). On the other hand, neither CBN nor CBD were found to affect food and water consumption over a range of i.p. doses up to 80.0 mg/kg (24). However, in this latter study, CBD, but not CBN, was found to enhance the suppressive effects on consummatory behavior produced by delta-9-THC.

The general findings of cannabinoid-induced suppression of consummatory behavior stands in stark contrast to the findings that marihuana or hashish will increase the human appetite for food (1, 31). Several possible explanations have been offered to account for this discrepancy. Sofia and Barry (60) have suggested that since pure delta-9-THC has not been used with humans, the appetite-stimulant effect of marihuana might be due to a constituent other than THC. The recent findings regarding CBN, CBD and CBC reported above (24, 57) seem to make this suggestion less likely. It has also been suggested that, since most animal studies have not taken continuous measurements of consummatory behavior, increases in consumption may

have been overlooked. However, in recent experiments with rats where such continuous measures have been taken (32, 60), dose-related delta-9-THC decreases in food and water intake have been confirmed. There is some evidence (28) to support the contention (22) that the discrepancy between animal and human consummatory behavior is due to the higher cannabinoid doses, relative to body weight, used in animals than in humans. Furthermore, the possibility that the discrepancy is related to humans' adaptation to a long-term deprivation regimen whereas most animals used as either nondeprived or acutely deprived has also received empirical support (29). Nevertheless, the discrepancy between animal and human experiments is inadequately explained. There is, of course, the possibility that the differences are due solely to between-species differences. If so, consummatory behavior will stand as a rare instance in which animal research with cannabinoids has not served reliably as a predictor of cannabinoid effects in humans.

AGGRESSIVE BEHAVIOR

If aggression is taken as a uniform behavior of threatening or attacking another animal, then conflicting findings regarding the effects of cannabinoids on aggressive behavior exist in the literature. However, a variety of procedures has been used to study the aggressive interactions between animals under the influence of cannabinoids, each of which tends to involve a different kind of aggressive behavior. In fact, when separated by aggression paradigms, the literature regarding cannabinoid effects on aggressive behavior is quite consistent. In general, the conclusion from both the last Marihuana and Health report (47) and a recent extensive review of the cannabis and aggresion literature in animals (2) is that cannabinoids suppress aggressiveness in nonstressed animals but increase stress-induced aggression. While one recent study (51) has demonstrated an increase in agression following long-term administration of THC to rats which were not apparently stressed, the above conclusion applies to the acute cannabinoid experiments on animal aggressiveness which have appeared since the last report. For the sake of discussion, the new experiments will be divided into categories of stress-induced and nonstress-induced aggression, with the latter category being subdivided into isolation-induced aggression, competitive aggression and predatory aggression.

Stress-induced aggression

As indicated, when stressed animals are put under the influence of cannabinoids the usual outcome is an increase in aggressiveness. This outcome seems to be independent of the nature of the stressor used. Increased aggression under cannabinoids has been reported for such stressors as: starvation (13), low temperature (12), REM sleep deprivation (5, 11), withdrawal from morphine (10), septal lesions (21), electric shock (9) and most recently, ovariectomy (54).

Takahashi and Karniol (61) have investigated the interaction between CBN and delta-9-THC with respect to stress-induced aggression. Generally, this experiment produced results comparable to a simi-

lar previous investigation of the interactive effects of CBD and delta-9-THC on aggression induced by REM sleep deprivation (37). Intraperitoneal injections of 20.0 mg/kg delta-9-THC and 80.0 mg/kg CBN induced aggressiveness in the stressed rats. Interestingly, however, when the same doses of CBN and delta-9-THC were administered together, the amount of aggressiveness was less than that produced by delta-9-THC alone (61).

Isolation-induced aggression

Several experiments have shown that delta-9-THC and cannabis extract will suppress isolation-induced aggression in rats which have not also been subjected to stress (e.g., 21, 58). Other studies have shown that this cannabinoid-induced suppression of aggression is not a result of motor impairment (38) nor does it exhibit tolerance (63).

The interaction between delta-9-THC and CBD on isolation-induced aggression was investigated this year in mice (62). Intraperitoneal doses of 2.5 mg/kg delta-9-THC and 40.0 mg/kg CBD individually suppressed aggressiveness although the interaction between these two cannabinoids was not significant.

Competitive aggression

Recent findings are in accord with previous results (34, 52, 64, 65) showing that delta-9-THC reduced dominance and social competition in animals. For example, Cutler et al. (18) administered cannabis resin to mice in i.p. doses ranging from 4.0 to 100.0 mg/kg, then placed the mice with unfamiliar partners. These researchers found that the drug did not affect nonsocial behavior, social investigation or sexual behavior. However, dose-related increases in immobility and flight relative to aggression were obtained.

Ely et al. (23) demonstrated the importance of the existing social structure in their examinations of cannabinoid effects on animal aggression. Doses of 0.5, 2.0 and 20.0 mg/kg of delta-9-THC were intravenously injected into mice whose dominant or subordinate status in their colonies was either relatively stable or whose dominance was threatened either by a rival or an intruder. In the stable colonies the only behavioral change noted was a limited period of reduced activity by the dominant males. Dominant mice confronted with a rival exhibited a reduction of activity and a consequent loss of their dominant status. Dominant mice confronted with an intruder made fewer attacks on the intruder than nondrugged dominant mice, but their aggressiveness returned to the pre-drug baseline level after 24 hours.

Dose effects of delta-9-THC on aggressive behaviors of resident and intruder rats were examined by Miczek (50). This investigator varied i.p. dose level from 0.125 to 4.0 mg/kg and found that as the dose was increased, attack and threat behaviors of the dominant resident rat decreased. Only at the highest dose level of 4.0 mg/kg did delta-9-THC interfere with the defensive and submissive behaviors of the intruder.

Predatory aggression

Research appearing before the last report (47) supported the conclusion that cannabinoids reduce predatory aggression in nonstressed

animals (2, 21, 48). Although one study (4) indicated that THC could produce muricidal behavior in rats which did not previously display such behavior, it was not possible to conclusively determine whether stress induced by food deprivation or the administration of the cannabinoid over a 40-day period was responsible for this result. However, a recent study by Miczek (51) indicates that the long-term administration period may have been the crucial factor. This investigator found that during an administration period of 60 days, previously nonmuricidal rats given sufficient food and water so as not to lose weight and an intraperitoneal delta-9-THC dose of 10 or 20 mg/kg/day developed mouse-killing behavior.

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CHAPTER 5

Preclinical Effects: Learned Behavior

A review of the previous four Marihuana and Health reports (40, 41, 42, 43) reveals that an extensive array of procedures and contexts have been used experimentally to study the effects of cannabinoids on the performance of learned behavior in animals. These preclinical behavioral experiments have provided a framework for, and guided the design of, subsequent human experimentation. Compared to previous years, only a few experiments pertaining to cannabinoids and learned behavior have appeared this year. By and large these more recent experiments confirm previous findings; no particularly novel procedures have been employed nor have there been dramatically unpredictable results. In part, the decrease in activity in cannabinoid preclinical animal research on learned behavior is one sign of an increase in human cannabinoid-learning investigations.

Several detailed taxonomies of learned behavior are possible. However, for the purposes of the present report, learned behaviors will be categorized into those involving: avoidance learning and aversive control; reinforcement schedules and maze learning; and discrimination learning.

AVOIDANCE LEARNING AND ADVERSIVE CONTROL

Whether or not cannabinoids enhance, depress or fail to affect the acquisition of avoidance behavior depends importantly on the cannabinoid time-course of action (45) and dose (22), as well as on the particular cannabinoid (28) and type of avoidance task used (52). However, when the behavior investigated is performance, rather than acquisition, of a learned avoidance task, cannabinoids have been reliably found to have disruptive effects (e.g., 9, 27, 28, 47).

Additional reports of cannabinoid-induced impairment of established avoidance behavior have come from Tayal et. al. (53) and Pryor and Braude (51). In the latter study (51), it was further reported that delta-9-THC had a more than additive interaction with phencyclidine, over a wide range of doses for both drugs, in impairing conditioned avoidance behavior. The Tayal et. al. (53) experiment also found that tolerance develops to the disruption in avoidance performance induced by an alcoholic extract of cannabis. This finding of tolerance confirms and extends previous reports of cannabinoid tolerance development under learned avoidance tasks (e.g., 27, 39). However, no new research has appeared to add to the finding (47) that delta-9-THC is cross tolerant with ethyl alcohol but not with morphine or chlorpromazine in a shuttle box avoidance task.

With respect to aversive control situations other than avoidance learning, there have been several reports that cannabinoids reduce the

conditioned emotional response of animals to a stimulus previously associated with an unavoidable electric shock, regardless of whether an appetitive or aversive situation is used to maintain baseline responding (e.g., 23, 27). The usual interpretation given to this finding is that cannabinoids act to reduce fear or anxiety. However, a fear-reduction interpretation does not always gain support from research with humans (50).

Moreover, Ferraro and Bruce (16) have argued that previous conditional emotional response experiments have been, in part, confounded by drug-state changes which occurred between the training and testing phases of these experiments. Indeed, when they compared the conditioned emotional responses of rats who had received all of their training and testing under 2.0 mg/kg delta-9-THC (intraperitoneal injection) with nondrug control rats, delta-9-THC was found to increase the conditioned emotional response (14).

Another factor which may be considered to temper the interpretation that cannabinoids reduce fear in aversive control situations is that delta-9-THC has been found to have an analgesic effect in animals (35) and humans (48, 49). This was demonstrated by Dykstra and McMillan (12) who used a titration procedure to determine the intensity at which monkeys would maintain a continuously applied electric shock. It was found that an injection of 15.0 mg/kg delta-8-THC caused the monkeys to adjust the shock to a higher intensity than they had in the absence of the drug.

In still another aversive control context, Corcoran et al. (8) have extended previous findings that delta-9-THC (14) and hashish extract (7) produce "bait shyness" in rats when paired with novel tastes. In the Corcoran et al. (8) study, delta-8-THC, CBD, and cannabiderol (CBG) all produced bait shyness. However, cannabichromene (CBC) did not produce a conditioned taste aversion in this aversive control situation.

REINFORCEMENT SCHEDULES AND MAZE LEARNING

Both operant and instrumental conditioning paradigms have been used to study the effects of cannabinoids on appetitively reinforced learned behavior in animals. In the operant conditioning context, schedules of reinforcement have received the most study. In the instrumental conditioning context, maze or alley learning has been the usual baseline for determining cannabinoid effects.

Following the outline established in the fourth Marihuana and Health report (43), experiments dealing with cannabinoid-reinforcement schedule interactions will be categorized in two major types: Type I experiments which focus on changes in schedule controlled responses, and Type II experiments in which such responses merely provide a baseline for the study of drug-related parameters.

The bulk of the earlier cannabinoid research with reinforcement schedules was of the first type (cf., 40, 41, 42, 43). What little research of this type there has been in the past two years (e.g., 9, 20, 55) has mainly tended to replicate and confirm the findings from the earlier research even where more complicated reinforcement schedules have been used (2). Taken all together, the research demonstrates that

behavior under reinforcement schedule control is reactive to delta-9-THC and delta-8-THC as well as to other constituents of cannabis (10, 21). In general, such behavior is depressed in a dose-related manner by cannabinoids, although under schedules which tend to generate low response rates, a bi-phasic dose-response function or an alternation between periods of no responding and increased rates of responding are sometimes observed.

Although only limited attention has been given to the effects of cannabinoids on the acquisition and extinction of operant behaviors (18), the now very extensive literature on the relationship between cannabinoids and performance of schedule controlled responses has stimulated the use of such responses as baselines in Type II studies of drug-related parameters.

Among other things, reinforcement schedule baselines have been used in the past two years to study: Between-cannabinoid comparisons (36); cross-tolerance between cannabinoids and other drugs (47); and differences between drug vehicles and routes of cannabinoid administration (1, 15, 17). An operant paradigm has also been used to investigate the interaction between delta-9-THC and cannabidiol. Davis and Borgen (10) found that intraperitoneal injections of 3.0 mg/kg delta-9-THC suppressed schedule controlled responding in rats while 25.0 mg/kg CBD did not. Similarly, intramuscular injection of 1.0 mg/kg delta-9-THC suppressed responding in pigeons while 50.0 mg/kg CBD did not. However, when animals were pretreated with their respective CBD doses, the THC induced suppression of responding was reduced.

An instance of the Type II reinforcement schedule experiment was recently performed by Dykstra et al. (13) These researchers injected pigeons responding under variable interval, fixed ratio, and fixed interval schedules with a range of delta-9-THC and SP-111 doses (.3 to 18.0 mg/kg intramuscular injection administered either one or two hours before the start of the experimental session). SP-111 as a water soluble ester of delta-9-THC which bears a basic amino function (56). Both drugs produced a dose-related suppression of reinforcement schedule responding although delta-9-THC was three to six times more potent than SP-111 and had a faster time of onset.

A large number of both types of reinforcement schedule experiments have investigated the development of tolerance under the cannabinoids (e.g., 1, 2, 20, 36, 38, 47). These experiments have uniformly shown that tolerance readily develops in animals to cannabinoid-induced suppressant effects on operant responding. However, two studies have shown that, in this situation, tolerance development to delta-9-THC is due to the animals responding under the influence of the drug rather than to the mere exposure of the animals to delta-9-THC (5, 38). Moreover, Frankenheim (20) observed that repeated i.p. injections of delta-8-THC (10.0 and 17.8 mk/kg) tended to increase the sensitivity of rats to a response rate-increasing effect of the drug under a differential reinforcement of low rate schedule of reinforcement. This increased sensitivity was likened by Frankenheim (20) to the reverse tolerance sometimes reported for marihuana effects in humans.

Compared to operant reinforcement schedule research, the effects of cannabinoids on the acquisition and performance of instrumental maze

or alley-way responding have not received extensive study. A Canadian study, not yet published, has found that permanent impairment of maze learning ability in rats occurred following six months of treatment with oral doses of either ethanol or cannabis extract. While the doses of THC and alcohol were both relatively high (20 mg THC/kg) the authors point out the animals were visibly intoxicated for "only about four hours after each dose, gained weight normally and were in good general health throughout the experiment." Based on the degree of intoxication, they argue that the research may be relevant to possible learning impairment under conditions of unusually heavy human use (57). Based on previously published literature, it may be concluded that the cannabinoids impair reinforced and latent learning in a variety of instrumental conditioning situations including the Y maze, T maze, Lashley III maze and straight alley (11, 29, 44, 46, 54).

DISCRIMINATION LEARNING

The effects of cannabinoids on discrimination learning were reviewed for the first time in the previous Marihuana and Health report (43) under two subtopics: 1) the effects of cannabinoids on the performance of discriminations based on exteroceptive stimuli, and 2) the acquisition of stimulus control of behavior based on the presence or absence of cannabinoids.

As there have been few experiments published since the last report which describe the effects of cannabinoids on discrimination learning with exteroceptive stimuli, only a brief summarization of the existing literature will be made herein.

In general, the effects of cannabinoids on established stimulus discriminations are influenced by the same variables as determine the effects of other psychotropic drugs on discrimination performance (cf., 43). More specifically, disruption of discrimination performance by cannabinoids is more likely if the discrimination is complex rather than simple and if the discrimination is successive rather than simultaneous. The typical cannabinoid-induced disruption of discrimination performance is the result of dose-related decreases in responses to the stimulus associated with reinforcement and corresponding increases in responses to the stimulus associated with nonreinforcement. Finally, and in accord with the effects of most other psychotropic drugs, during generalization testing delta-9-THC reduces total response output but does not typically alter the slope of the generalization gradient.

It is now well established that animals can learn to discriminate between the presence of cannabinoids and a vehicle-control solution (3, 4, 19, 25, 31, 32, 33, 37). Jarbe et. al. (33) used an experimental procedure which is prototypic of research on this topic. Gerbils trained in a T maze were required to make discriminative choices based on whether delta-9-THC or drug vehicle alone had been injected prior to the training session. As is the usual outcome in cannabinoid stimulus studies of this sort, Jarbe et. al. (33) found that the delta-9-THC discrimination was acquired in a dose-related manner (from 0.5 to 16.0 mg/kg, i.p.), Furthermore, decreasing the dose or increasing the injection-test interval from that used in training led to a decrease in delta-9-THC associated choices. One final aspect of this study which

is unique is that pentobarbital (20.0 mg/kg) interacted in a more than additive fashion with delta-9-THC to determine drug versus control solution choice responses.

The delta-9-THC discrimination paradigm has also been used recently to compare the potency of different routes of drug administration (3, 32). As compared to intraperitoneal administration, delta-9-THC administered orally or by inhalation had stronger stimulus properties while lesser stimulus properties were manifest after intravenous administration of delta-9-THC.

Although some quantitative differences exist, it now appears that the stimulus properties of delta-9-THC are interchangeable with delta-8-THC, 11-OH-delta-8-THC, cannabis extract, and hashish smoke (3, 32). However, neither CBD or CBN seemingly produce THC-like stimulus properties (32). Furthermore, a wide range of drugs from several pharmacological classes have been shown not to be interchangeable, in terms of stimulus properties, with delta-9-THC. Thus, there is support for a hypothesis that the active cannabinoids may have a unique mode of pharmacological action.

One final aspect of the cannabinoid-stimulus discrimination paradigm merits further study. Of concern is whether or not tolerance develops to the drug-stimulus properties of delta-9-THC. There have been three studies which address this concern. One study supports the development of tolerance (26), one provides indirect evidence supporting tolerance development (30), and finally, one provides data indirectly supporting a lack of tolerance development (6). Until additional experiments are performed it seems appropriate to conclude tentatively that a slow, and perhaps partial, tolerance develops to the stimulus properties of delta-9-THC.

State-dependent learning refers to the phenomenon that animals perform better if trained and tested under the influence of a drug than if a drug-state change occurs between the training and testing phases of an experiment. State-dependent learning has been shown for delta-8-THC and delta-9-THC (cf., 45). However, it is not clear from the THC literature whether or not symmetric disruptive effects are obtained between a change from a drugged to a nondrugged state (D-ND) and a change from a nondrugged to a drugged state (ND-D). Both symmetric and asymmetric state-dependent effects have been reported for THC (24). In the case of asymmetric effects, a change from the ND to D state (22). Johansson et al. (34) have shown that delta-8-THC will reliably induce asymmetric state dependency of this latter type if animals are first made tolerant to the acute disruptive effects of the drug.

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CHAPTER 6

Preclinical Chronic Effects: Unlearned and Learned Behavior

There is no unequivocal answer to the question of whether or not tolerance develops to cannabinoid-induced effects on unlearned and learned behavior. In certain response systems, tolerance clearly develops and is characterized by its rapid development and large magnitude. Indeed, in the past two years tolerance has been demonstrated for both unlearned and learned responses in a range of animal species under a variety of drug conditions in studies examining: unlearned motor responses in rats (4); spontaneous activity in mice (3); conditioned avoidance performance in rodents and monkeys (30, 39, 46); analgesia in dogs (31); and reinforcement schedule performance in pigeons, monkeys and rats (2, 5, 21, 32).

In addition to demonstrations that tolerance to the cannabinoids can develop in unlearned and learned behavioral situations, there have been several experiments which serve to elucidate some of the determinants, both pharmacological and extrapharmacological, of tolerance development to the cannabinoids. These latter experiments encompass a wide variety of situations and parameters and, in some instances, suggest constraints on the generality or pervasiveness of tolerance to the cannabinoids. The studies described below are representative of these experiments.

Abel et al. (1) have shown that tolerance to the effects of delta-9-THC on reinforcement schedule responding develops in pigeons at about the same rate after intramuscular, intravenous, or peroral administration. Tolerance also follows a similar course for delta-9-THC and its metabolite 11-OH-delta-9-THC (32). However, Fernandes et al. (13) have suggested that CBD interacts with THC to enhance the tolerance development to THC.

Barns and Fried (4) have shown that the age of the subject at the time of first exposure to delta-9-THC interacts with later tolerance development. Rats first received delta-9-THC when immature developed tolerance more rapidly as adults than did rats who were adults when first drugged.

Rate of tolerance appears to depend as well on: the amount of prior training on a learning task (40); and the type (39), parameter values (19, 24, 30), and complexity of the learned task (16, 43). In general, as the amount of prior training is decreased and the difficulty of the learned task is increased, tolerance develops more slowly or does not develop at all. Another behavioral variable that seems to determine the rate of tolerance development is the behavioral consequences produced by delta-9-THC (14, 36). For example, in one experiment (36) tolerance developed to delta-9-THC much more rapidly if delta-9-THC acted to increase the number of shocks received by rats working

under a conditioned avoidance task. In this same learning context, it appears that the development of delta-9-THC tolerance in appetitive reinforcement situations is facilitated if animals are given the opportunity to respond under the influence of the drug rather than being given mere exposure to the drug. This latter finding has been reported for rats (7), pigeons (5), monkeys (35), and chimpanzees (18).

On the basis of findings such as the above, Ferraro (15) has followed the lead of others (12, 25) in proposing a behavioral model of marihuana tolerance. The essence of this position is that learning or drug-behavior interactions account, in part, for some of the characteristics of tolerance development to delta-9-THC. The pharmacological mechanism underlying tolerance development to the cannabinoids is not definitely known (cf., 37). However, there is evidence which suggests that the development of tolerance to delta-9-THC may proceed by more than one pharmacodynamic mechanism of action. For example, Anderson et. al. (3) found that both the time of onset and the duration of tolerance to delta-9-THC differed in mice with respect to drug effects on intestinal motility, temperature, and locomotor activity. As these researchers concluded, it seems unlikely that any one mechanism, such as metabolic tolerance, could account for the obtained differences in tolerance development over so wide a range of response systems. Other experimenters have provided data which suggest that delta-9-THC tolerance is not solely metabolic or drug distributional (10, 38). Obviously, additional research will be necessary in order to specify just what pharmacodynamic and learning factors are important in determining the development of tolerance to marihuana.

Admittedly, it is not possible to make direct comparisons between different cannabinoid tolerance experiments since they often differ in nonsystematic ways with respect to such variables as number, level and distribution of drug doses, behavioral task and species of subject. Nevertheless, it must be noted that the literature contains a fair number of experiments where a lack of tolerance development to the cannabinoids has been reported. This result has been found for rodents in such situations as: open-field behavior (42); isolation-induced aggression (11); food and water intake (23, 44); and discrimination learning based on exteroceptive (20) or drug-produced stimuli (6). By contrast, Frankenheim (22) has recently reported that repeated injections of delta-8-THC produce an increased sensitivity to some of the effects produced by this drug on reinforcement schedule-controlled responding in rats. This increased sensitivity was likened by Frankenheim (22) to a reverse tolerance effect.

With respect to other chronic effects of the cannabinoids, two experiments have failed to find any residual effects on learned behavior following discontinuance of delta-9-THC previously administered for 150 consecutive days (18) or aperiodically for seven months (17). And, with the exception of one experiment (41), animals have not been observed to self-administer cannabinoids. More specifically, monkeys do not self-administer delta-9-THC after receiving the drug for a month or when offered it as a substitute for cocaine (26). Rats forced to drink cannabis extract or hashish suspensions for long periods of time (up to 126 days) reject the drug in favor of a control solution

(9, 33). Finally, mice are reluctant to consume food pellets containing delta-9-THC even after subsisting on the pellets for over two months (34).

It is noteworthy that no behavioral symptoms of abstinence or withdrawal were reported in the above experiments at the termination of the forced drug regimens used (cf., 26, 33). One further experiment by Chesher and Jackson (8) reported the absence of an abstinence syndrome after withdrawal of cannabis extract administered in oral doses equivalent to up to 80.4 mg/kg delta-9-THC for 11, 13, and 28 days. In this study, mice were tested for their convulsive thresholds to pentylenetetrazol between six hours and six days following termination of the cannabis drug regimen. No differences were obtained between drug and control animals.

Despite the above evidence to the contrary, there were two reports last year that were suggestive with respect to delta-9-THC-produced dependence and abstinence symptoms (29, 45). In the better controlled of these experiments (45), rats were administered naloxone hydrochloride after a five-week pretreatment period with delta-9-THC (8.0 to 32.0 mg/kg, intraperitoneal injection). The rats exhibited narcotic-like withdrawal symptoms including diarrhea, teeth chattering and "wet dog" shakes. Two additional experiments published this year (27, 28) demonstrated that delta-8-THC and delta-9-THC, but not CBD, reduce the abstinence symptoms precipitated by naloxone hydrochloride in morphine-dependent rats. In the first of these (27), delta-9-THC doses of 5.0 and 10.0 mg/kg administered by the intraperitoneal route one hour before naloxone administration significantly reduced the frequency of wet shakes and diarrhea in the morphine treated rats. On the basis of their data, Hine et al. (27, 28) concluded that the tetrahydrocannabinols may have some therapeutic utility in clinical narcotic detoxification programs.

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CHAPTER 7

Human Effects

ACUTE EFFECTS

A person ingesting or smoking cannabis experiences a fairly predictable sequence of physiologic and psychologic changes which last a few hours and then gradually disappear. Although dose administered and individual differences in personality, expectations, setting and past drug experience all contribute to varied consequences from a given dose of cannabis, the variability in acute effects from cannabis seems no greater than with any other psychoactive drug. A number of reviews and collections of papers have appeared during the past year which attempt to cover the vast amount of information accumulating about the acute and chronic effects of cannabis (7, 27, 43, 70, 82, 114). Some authors have attempted to consider the research findings in the context of political-social decisions (43, 135) and point out the lacunae in the data as well as the well established facts (43). The continuing research efforts this past year have attempted to fill some of the gaps. Emphasis has been placed on the chemistry of cannabis constituents, less obvious effects such as hormonal changes and the initial studies of acute drug effects in populations other than those made up of self-selected marihuana users.

Activity of natural and synthetic cannabinoids

Detailed pharmacokinetic studies of delta-8-THC in man using mass fragmentographic techniques indicate a similar time course and clearance pattern to that seen with delta-9-THC (103). A very rapid alpha phase was followed by a slower phase. While blood levels did not always predict physiological and psychological effects, they paralleled heart rate changes well.

DMHP, a synthetic cannabinoid, differs from delta-9-THC by having a double bond in the 6a, 10a positions. Intravenous administration in man produced profound cardiovascular effects but only minimal psychological effects (102). As is the case with natural cannabinoids, hydroxylation seemed to be the major metabolic pathway.

Metabolism of cannabinoids and biochemistry

Metabolites.—Although studies of a major metabolite of delta-9-THC, 11-hydroxy-THC, indicate it is pharmacologically active, some question remains whether it is the only metabolite or whether delta-9-THC needs to be hydroxylated to 11-hydroxy-THC before the THC is active (72). In an attempt to clarify these issues, Hollister sorted people into fast and slow hydroxylators on the basis of antipyrine

and phenylbutazone plasma disappearance rates. THC and these drugs are metabolized by the same liver microsomal enzyme system (169). There was no difference in speed of onset, intensity or duration of effects after intravenous injection of delta-9-THC when the two groups were compared (72). Such results suggest 11-hydroxy-THC may not be the sole source of delta-9-THC effects. Another group of investigators found 11-hydroxy-THC to leave the plasma more rapidly than THC, suggesting THC may, in fact, be more potent (133).

A number of additional marihuana metabolites have been reported in a series of studies (83, 84, 85) and for the first time, unchanged delta-9-THC was identified in the urine using conventional thin layer chromatographic techniques in amounts estimated at .01–.005% of the dose (74). New extraction procedures revealed a previously ignored fraction containing abundant metabolites (83) including many polar metabolites (84). The exact identity and activity has yet to be determined. In a review of structure activity relationships of cannabinoids in man, Hollister concluded that the potency of the THC molecule is altered by changing length of side chains, or by metabolic hydroxylations. No material has yet been formed in nature in cannabis itself or in THC metabolites which differ qualitatively from THC (71). There is now evidence indicating the human small intestinal mucosa, as well as the liver, can hydroxylate THC (59).

Cannabinoid interactions.—Studies of the possible interaction between delta-9-THC and the other two major cannabinoids of marihuana—cannabinol (CBN) and cannabidiol (CBD)—are not completely consistent in their conclusions. Hollister found only slight interaction between THC and CBD. After CBD, there was a delayed onset and prolonged effects of THC that were slightly more intense (73). The magnitude of the interactions was so small as to be clinically insignificant. However, other experiments in man with different samples of marihuana plant material containing varied amounts of CBN and CBD found differences in effects, possibly due to differing proportions of CBN, CBD and THC(18). A subsequent study by the same group found large doses of CBD to block many of the effects of THC (86). A possible complicating factor in cannabinoid interaction studies is the issue of instability of various synthetic and naturally occurring cannabinoids (165).

Interactions with other drugs.—Besides CBD and CBN, other drug interactions with THC have been investigated in man. Secobarbital and smoked marihuana had additive effects on subjective responses and psychomotor impairment (32). Subjects had difficulty distinguishing 150 mg of secobarbital from 25 micrograms of THC/kg. When amphetamine and smoked marihuana were combined, additive effects of heart rate and blood pressure and subjective symptoms were observed, but no interaction effect on psychomotor performance was found (47). Based on the assumption that THC interferes with cholinergic brain mechanisms, physostigmine decreased the tachycardia and conjunctival injection, but had little effect on psychological changes (54). Little potentiation of narcotic drug effects was noted in a study evaluating THC as a pre-anesthetic agent (77). Animal studies indicate that whatever the drug combination the depressant effects of THC tend to predominate (138).

Assay techniques.—A great deal of effort has gone into the development of practical assays of cannabinoid levels in man. Such measures are needed not only for research purposes, but would be useful clinically and in law enforcement (particularly in cases where intoxication while driving an automobile is an issue). A number of techniques using saliva and TLC with mass spectrometry (81), radioimmunoassay of blood and urine (105, 160), and gas chromatography of blood (106) have been reported but still are not sufficiently sensitive, specific and reliable for widespread practical application. The tight binding of THC to plasma protein (170) is only one of the many problems in the development of sensitive reliable tissue level assays (cf. Analytical Techniques, Detection).

Cardiovascular effects

Cannabis has long been known to have marked cardiovascular effects (21, 143). Last year's report reviewed some preliminary data which resulted in some expressed concern about electrocardiographic changes during acute intoxication. The subsequent publication of a number of studies where cardiovascular dynamics were studied some time after administration of large doses of THC indicates that cannabis produces only minimal EKG changes in young healthy subjects (77, 8, 22, 104). Nonspecific P or T wave changes are most commonly noted. Occasional premature beats also occur. Tachycardia continues to be the most common and prominent physiological response to acute doses (145). In a study of prolonged administration of oral doses of 30 mg delta-9-THC given every four hours, heart rate slowing and blood pressure drops developed (8). Blunting of peripheral vascular reflexes developed along with plasma volume expansion. Although tolerance developed to the orthostatic hypotension, the supine hypotensive effects persisted throughout the period of drug administration. These changes commonly seen in laboratory animals but not previously noted in man suggest a biphasic action of THC in humans with an increase in sympathetic activity involving the heart and peripheral blood vessels at low doses and a centrally mediated sympathetic inhibition at higher doses (65). The slightly increased supine blood pressure would be consistent with this mechanism (22, 77, 104). Forearm blood flow increases and total peripheral resistance decreases slightly with acute doses (104, 77) consistent with beta-adrenergic stimulation. The great individual variability in response to large intravenous doses has, however, led one group to suggest an indirect episodic activation of the sympathetic system secondary to psychological arousal in addition to the beta-adrenergic stimulation (104). Cardiovascular and psychological mechanisms of action may be independent as is suggested by the observation that DMHP, a synthetic cannabinoid, produces profound cardiovascular but few psychological effects (102).

A series of reports on the cardiovascular effects on cannabis smoking in persons with coronary disease are consistent with the preliminary report cited last year (137, 4, 3). Smoking either marihuana or high nicotine cigarettes decreased exercise performance prior to the onset of angina by increasing myocardial oxygen demand and decreasing myocardial oxygen delivery (4). Cardiovascular hemodynamics were evaluated by echocardiography (137). After marihuana, stroke

index decreased and ejection fraction was greater. Carboxyhemoglobin made for some changes after both marihuana and placebo. These studies demonstrate that marihuana effects may differ in individuals with pre-existing disease than in normals. Most research studies thus far have, of course, been done on youthful selected, normal volunteers.

Pulmonary effects

Because smoking is the most common means of cannabis consumption in this country, the effects of cannabinoids and marihuaa smoke on pulmonary function has been of continuing interest. The fourth Marihuana and Health report described bronchodilating effects with possible therapeutic implications after marihuana smoking. Previous reports have described mainly adverse findings in frequent chronic cannabis smokers including bronchitis, obstructive pulmonary defects, and chronic cough (62).

Two groups publishing the promising reports described last year have continued and extended their studies (149, 156, 157, 168). Acute administration of either smoked marihuana or oral doses of THC produced statistically significant increases in bronchodilation and reversed experimentally induced bronchospasm in young adults with bronchial asthma (156, 157, 168). Indications are that the mechanism is independent of beta adrenergic or antimuscarinic effects (149). In contrast to these promising reports, a British group (34, 58) found that measures of forced vital capacity, peak expiratory flow rate and other clinically useful measures of pulmonary function did not improve in a group of patients with reversible airway obstruction given 10 mg doses of oral THC. One possible reason for these discrepant findings may be that the groups (149, 156) reporting cannabis-induced bronchodilation are using whole body plethysmography, an exceedingly sensitive measure that will detect very small changes in pulmonary function, whereas the less optimistic reports come from a group using less sensitive, although clinically relevant measurement techniques.

Chronic smoking may produce different and less useful effects than acute administration as indicated by pulmonary function changes during periods of chronic administration (109). Mendelson found significant impairments in pulmonary function tests (vital capacity, or FEV 1.0) in a group of chronic marihuana smokers (109). Further reduction in pulmonary function test performance developed during this study in which the volunteers smoked three to ten marihuana cigarettes daily for 21 days. An outpatient study of young adults with varying tobacco cigarette habits found more improvement in pulmonary function during an eight week period of no smoking in the cannabis smoker subgroup (5). An *in vitro* study suggests that the water soluble components of marihuana smoke may contain substances toxic to the defense network of the lung other than delta-9-THC or other cannabinoids (31). Studies using high doses of THC given intravenously noted only modest changes in minute ventilation and the ventilatory response to CO2 equivalent to that produced by 5 mg doses of morphine (77, 104).

A study of the respiratory effects of smoked marihuana and orally ingested delta-9-THC has examined the effects of the drugs on the respiratory response curve. Both the synthetic and natural material

produced a respiratory depression in a group of previously chronic users. Although the effect was found to be slight, the authors recommend further study because of the possible relevance of this effect to patients with chronic lung disease or central nervous system impairment of respiratory regulation (172).

Endocrine and metabolic effects

The report of depressed plasma testosterone levels in chronic marihuana smokers (98) and the report of a failure to find such a change in marihuana smokers receiving the drug daily over a 21-day period (110) have led to further studies and discussion (55, 93, 96, 97, 99, 100, 101). Kolodny has reviewed the numerous problems confounding the study of the hypothalamic-pituitary-testicular axis in man (96) and discusses possible biologic implications of lowered testosterone levels. He presents data (97, 100) showing significant drops in plasma testosterone levels and luteinizing hormone levels two and three hours after smoking a single marihuana cigarette. In a chronic administration study, subjects showed no significant drop in levels after four weeks of daily marihuana smoking; but, then, with continued smoking they had significant drops in luteinizing hormone, followed by falling testosterone levels and follicle stimulating hormone levels. Thus, the data from research finding no marihuana-related hormone changes (93, 110, 144) are quite consistent with studies that do (97, 98, 100) if the different time periods of marihuana use are taken into account. The biological significance of these changes is unclear and Kolodny is appropriately cautious in his interpretation of their importance (96). In most cases the plasma hormone levels remain within the usually accepted normal limits. Such alterations might be expected to be more important for prepubertal or pubertal males or males with already impaired sexual functioning. There might also be adverse effects on sexual differentiation of the fetus of mothers using cannabis. In the absence of clinical evidence for these consequences, such concern is at present speculative.

One surgeon has attempted to link such hormonal changes to the development of gynecomastia in male marihuana users (66, 69). He was able to stimulate the development of rat breast tissue by delta-9-THC administration (66). Other investigators (101) have not found changes in serum prolactin levels in men given THC experimentally. The absence of prolactin changes is surprising since many centrally acting drugs alter prolactin levels. The reported gynecomastia was postulated to result from a prolactin dependent mechanism.

In last year's report a study described glucose intolerance in a small group of subjects given intravenous doses of delta-9-THC (75). A lower dose of THC given a smoked hashish had no effect on blood glucose though blood lactic acid decreased (129). Glucose efflux from human erythrocytes was inhibited by THC and cannabidiol, suggesting some drug effects on glucose transport mechanisms (146). It would, however, be quite speculative to try to relate these changes to the craving for sweets often reported by cannabis users.

Sexual functioning

Reports discussed in the section on "Endocrine Effects" describe sex hormone changes related to cannabis use. Although anecdotal accounts

describe cases of sexual dysfunction possibly associated with such changes, properly controlled studies are needed to confirm them (96, 100). A number of accounts report enhanced sexual activity associated with cannabis use (11, 20, 51, 63, 93). However, the psychological, social and pharmacologic factors associated with sexual activity probably interact in complicated ways as is true with most other drug effects on sexual behavior (20, 93). For example, with cannabis, as with alcohol, dose is important. Small to moderate doses appear to be most effective as releasers of inhibitions (93). Larger doses and/or chronic use of marihuana may actually diminish sexual interest and potency in males. Adequate data elucidating the effect of marihuana use on sexual functioning are not yet available.

Neurological effects

Perceptual, cognitive and mood changes are presumably reflected in changes in nervous system activity. As with any psychoactive drug, however, simple one-to-one correlations between behavioral changes and brain activity are rare (78). The most important questions have to do with how long the effects persist: for hours, days, weeks or are they permanent?

Most of the new studies are extensions of or attempts to replicate findings reported last year. Smoked cannabis produces acute, reversible, dose-related changes in brain waves as measured by computer-analyzed EEG (49, 91). Following ordinarily used doses, the changes are modest, consisting mostly of alpha wave slowing and are not indicative of any particular pathology. Cannabis does not appear to have unique qualities among CNS active drugs as measured by scalp EEGs. Changes in EEG recorded from deep brain structures, consisting of slow wave and spiking activity, have not, however, been seen with any other drug (67). These changes have been well-described in monkeys. Similar changes have been reported in a small number of humans (67). The behavioral significance of these neurological changes is yet to be determined (78). A recent review of possible neural mechanisms of cannabis suggests the hippocampus and other deep structures may be important sites of action (41), at least in animals.

Scalp EEG and evoked potentials showed marked changes in subjects given very large smoked doses of THC or marihuana (158, 159). Alpha abundance increased with posterior slow wave activity becoming prominent. Ataxia, hypersomnia, increased deep tendon reflexes, tremor, tonic muscle contractions and myoclonus followed these 1 mg/kg doses of THC.

Loss of REM sleep appears to be a predictable effect of cannabis (158, 159). Total sleep time increases. Stage 4 or slow wave sleep is relatively unaffected. In this respect cannabis is unlike any sedative-hypnotic drug studied thus far (48). When the drug is stopped after a period of prolonged administration, REM sleep stage and eye movements show a marked rebound above baseline levels. In contrast to the relatively small changes in waking EEGs after the drug is given, sleep EEG changes are very dramatic and large—both when the drug is acutely and chronically administered (48).

Changes in the slow cortical potentials recorded from the scalp (contingent negative variation or CNV) after cannabis are of particu-

lar interest since this measure is said to be sensitive to changes in motivation and attention deployment, among other factors. A recent study of the CNV obtained somewhat different results from those reported last year (10). Like many neurophysiologic measures, it appears the CNV is far more complicated than was originally assumed. It appears the CNV may get larger or smaller after cannabis, depending on the level of intoxication, the task demands, the motivation of the subject and changes in attention. To view the cannabis-induced CNV changes as any direct measure of attention deployment or motivation is probably an oversimplification (10).

Effects on cell-mediated immune response

Conflicting opinions as to the possible effects of cannabis on the cell-mediated immune response continue to appear (148). In the fourth report, the observation that chronic marihuana users had decreased in vitro lymphocyte response to allogeneic cells and to a mitogen was described (118). This original observation has led to extensive in vitro and animal studies described elsewhere in this report. Related studies in humans published this past year provide partial support for the notion of an immune system or thymus-derived cell alteration in people who smoke marihuana (30, 118, 134). However, other investigators using an in vivo skin testing procedure found no evidence of impairment of cell-mediated immunity in chronic marihuana users (151). Marihuana smokers had less T cell response to phytohemagglutin stimulation and decreased PMN phagocytic capacity (134). The authors of the latter study caution that the clinical significance of these findings is uncertain. In possibly related in vivo studies, the white blood cells from both cannabis users and non-users showed similar dose-related inhibition of migration when exposed to THC and extracts of cannabis (147). Substances other than THC in the crude extract may have effects on this test system.

Administration of THC or cannabis to controlled populations, with before and after testing, is underway and may provide useful information in clarifying the etiology of the cell-mediated immune effects (125).

Other physiologic effects

Previous reports associated cannabis intoxication with decreases in intraocular pressure. The possible therapeutic implication of this unexpected effect is discussed in the section on therapeutic applications. More extensive studies in normal volunteer subjects indicate a non-dose-related pressure drop lasting from four to five hours (68). The magnitude of the eye pressure decrease (about 30%) was the same whether the person smoked one or 22 marihuana cigarettes. Effects on other aspects of eye physiology (acuity, refractive error, biomicroscopy, fundus changes, visual fields, ophthalmodynamometry, electroretinography and orthoptic evaluation) were minimal or absent. Other investigators concluded that the observed eye pressure decreases were more likely a consequence of drug-induced relaxation and sedation rather than specific cannabis effects on the eye, since other sedative drugs produced similar changes in eye pressure (52). Results of studies of the effects of smoked marihuana on galvanic skin response are consistent with drug-induced reduction in level of autonomic nervous sys-

tem arousal (25). However, recent findings seem to contradict this interpretation (cf. Therapeutic Aspects).

Intravenous administration of a water infusion of cannabis resulted in gastroenteritis, hypoalbuminemia, hepatitis, and many cardiovascular changes secondary in part to hypovolemia (131). It is not entirely clear what symptoms were cannabinoid effects or, more likely, the nonspecific effects of injected foreign plant material.

Acute effects on mental and psychomotor performance

As in previous years a host of studies have reported impaired functioning on a variety of cognitive and performance tasks while marihuana intoxicated. For the most part, impairments were dose-related. The investigators who gave the smallest doses generally reported the fewest effects. Impaired memory (9, 33, 38, 39, 167), altered time sense (9, 167) and decrements on performance on a number of tasks—such as those involving reaction time, concept formation, learning, perceptual motor coordination, attention and signal detection—are commonly described (9, 24, 25, 32, 35, 37, 115, 116, 119, 120, 121, 150, 162). A number of discussions of the locus of the memory impairment have appeared (33, 39, 164). There is a growing consensus that the memory defect is due to a storage problem rather than acquisition or retrieval. There has been concern that cannabis may increase the suggestibility of those using it. However, in laboratory studies marihuana smoking had no effect on hypnotic susceptibility (6).

Effects on sensory function

One of the more commonly reported effects of cannabis is a subjective change in sensation. A number of groups investigated drug effects on various aspects of sensory functioning. Although subjective impressions of changes in skin sensitivity are commonly associated with cannabis intoxication, no objective or measurable change in cutaneous sensitivity using a number of measures was noted (115). The decrease in auditory signal detection while intoxicated appeared to be due to a decrease in sensitivity rather than a change in criteria (120). This finding contrasts with the usual subjective reports of enhanced auditory sensitivity. THC given to patients suffering from pain demonstrated mild analgesic effects but 20 mg doses orally produced many unpleasant side effects—somnolence, dizziness, ataxia, blurred vision, etc. (126, 127). The experience of experimentally induced pain in normal subjects was also diminished by smoked marihuana (130). Pain secondary to spinal cord injury was decreased by cannabis use (42). The characteristics of preferred tone frequency were shifted while intoxicated (35).

Automobile driving performance

More evidence has accumulated indicating that driving ability and related skills are impaired by cannabis at doses likely to be commonly used in the United States (90, 89, 119, 44). Despite their commonly expressed belief that their driving ability is impaired when intoxicated (90, 163, 32), more cannabis users appear to drive today while intoxicated than was the case a few years ago. In limited surveys 60% to 80% of the users questioned reported driving soon after marihuana use (90, 154). The use of alcohol in combination with marihuana before driv-

ing was reported by 64% of one sample and during driving by 20% of the sample (90). As the risks of arrest for possession decrease, one might expect more users will take the chance of being caught while intoxicated and driving (154).

A more detailed report of a Canadian driving study discussed last year (89) has appeared (90). The data clearly demonstrate that marihuana in relatively low doses (cigarettes containing approximately 5 and 8 mg of THC) typically had a detrimental effect on driving skills and performance not only on a test course but also under more usual city driving conditions. However, as is true with alcohol, effects were not uniform with all drivers. Some, particularly at the lower dose, actually improved their performance. Thus, the problem of individual differences that has complicated developing and enforcing "drunk driving" laws will probably recur when discussions of the minimal allowable dose or blood level of cannabinoids come up.

Compared to most of the behavioral tasks studied in the laboratory, automobile driving is more complex. The relative importance of the various perceptual, cognitive and psychomotor functions in determining driving ability is not completely understood. For example, in some situations the cognitive impairment produced by cannabis may have only limited impact on actual driving performance due to concomitant drug-induced changes in risk acceptance or feelings of aggression. In a laboratory simulation of driving, cannabis-intoxicated subjects took longer to decide whether to pass another car seemed less likely to accept the risks of passing and seemed less aggressive than alcohol-intoxicated subjects (40, 45). Other laboratory simulator studies have found that, while some driving skills are relatively unaffected by marihuana, there is a dose-related impairment in the ability to attend to peripheral stimuli while driving (119). Such an impairment might interfere with a driver's response to a car suddenly emerging from a side street.

Because of the many inherent inadequacies of laboratory driving simulator studies (90), cannabis-related driving risks will ultimately have to be assessed on the basis of studies of actual accident rates for users compared to non-users. This has been difficult in the study of alcohol. It promises to be still more difficult with cannabis because of the difficulties of measuring tissue levels of the cannabinoids, the longer excretion times, the more complicated metabolism and the often combined use of cannabis and alcohol while driving, making the relative contribution of either drug uncertain (90, 154).

Flying an airplane demands still more complex skills than does driving. There is little information concerning possible pilot error or impairment in performance as a result of having used marihuana. A preliminary study has shown that under flight simulator test conditions experienced pilots showed marked deterioration in performance following smoking marihuana containing 6 mg. of THC (108). More detailed studies are planned to follow up these initial observations.

Nonpharmacologic determinants of subjective response

Sociocultural factors (128) appear to interact with such pharmacologic aspects as dose and route of administration so as to modify marihuana's subjective effects. Some of these factors were explored in

studies published this past year. Laboratory studies are often criticized because a sterile, scientific laboratory setting may alter the response to the drug so that findings have little relevance to more typical conditions of use. A group of subjects were randomly assigned to smoke marihuana (16 mg THC) and were tested either in a typical medical research laboratory or a private living room designed to facilitate a pleasurable drug experience (76). Although there were great differences between subjects in their subjective responses to the smoked marihuana, the effect of the very different settings was negligible. A similar study using only a subjective level of intoxication as an index of drug effects found a psychedelic environment was associated with greater intoxication at intermediate dose levels, but not at the highest (16 mg THC) dose employed (14). Another attribute of the setting in which cannabis is often used is the possible effect of other intoxicated friends on a person's "high." However, in a study testing the effects of modeling, subjects smoking marihuana for the first time were relatively unaffected by the presence of an actor modeling a marihuana high (17). The results of this study suggest that previous experience with cannabis is a complicated socialization process in which individuals learn from friends and others to discriminate and label various aspects of the drug state (17). The mood one is in before smoking is sometimes thought to interact with the drug effects to produce varied outcomes. A laboratory study found no difference in subjective response to low doses of smoked marihuana and no difference in level of anxiety in groups of subjects made anxious by exposure to laboratory stresses (136). Finally, in a study mentioned in last year's report, but which had not yet been published, it was found that the dose of cannabis consumed in an experimental laboratory setting was determined by many factors (size of cigarettes, past drug experience) other than pharmacologic potency of the drug (15). A similar study by the same group (14) found that controlling the amount of drug consumed in accord with its varying strength was difficult for subjects, again suggesting that nonpharmacologic considerations are important in affecting the amounts consumed.

CANNABIS AND PSYCHOPATHOLOGY

The association of cannabis use with psychiatric illness raises complex questions for which no completely satisfactory answers are yet available. Two reviews of past research point out the many methodological and theoretical shortcomings of existing work (64, 112). A variety of psychiatric disorders are clearly associated with the use of cannabis—however, whether the psychopathology is an antecedent to use, a consequence or a mere coincidence is still very much open to question. A best guess is that cannabis use like that of many other psychoactive drugs will sometimes be an antecedent, a consequence or coincidental to psychopathology, depending on the person and many other variables (112).

As is often true in medicine, the ambiguity in diagnostic classification and definition adds to the confusion concerning adverse psychological reactions associated with cannabis use. The following classification has been adopted in imposing some order on the literature (64, 112).

Acute panic anxiety reactions

The acute panic anxiety reaction has been noted by many reviewers to be the most common adverse reaction to cannabis use (64, 112). The symptoms and signs are usually exaggerations of normal cannabis effects more generally described by users. Anxiety is often focused on fears of "going crazy." This reaction appears most likely to occur in novices and after consuming more potent materials. Personality variables that make for poorer coping skills play a role. The symptoms diminish with authoritative reassurance or in a few hours when the immediate drug effects have worn off. A number of reports in the past year illustrate these considerations (1, 87, 117, 124, 127, 164, 166).

Patients with chronic pain (127) and depression (1,139) given low doses of THC in therapeutic trials had far more dysphoric and acute panic episodes than would be expected if the same doses were given to typically youthful cannabis users. These older people presumably found it difficult to accept the drug-induced mental changes as desirable. Younger but equally inexperienced "cannabis experimenters" often react similarly (164, 117).

Cannabis-induced mild paranoid feelings in student and "counter culture" users of marihuana are common and usually not a source of undue concern to them (87). About two-thirds of a student group and 95% of a counter culture group studied described suspicion of being subjected to a police raid or having friends tricking them while intoxicated. Inability to reality test concerning these suspicions was reported by over half of the subjects. Another field survey found that individuals with a tendency to use paranoid defense mechanisms experienced fewer acute anxiety reactions after cannabis (124). The authors thought that the more sophisticated defenses represented in paranoid functioning may be effective in preventing acute adverse reactions. The same study found that persons with high scores on the schizophrenia subscale of the MMPI tended to have more problems with adverse psychological reactions indicating (as have a host of previous studies) that pre-existing psychopathology is an important factor in such reactions.

Cannabis induced acute-brain syndrome or toxic delirium

The clinical features of the acute brain syndrome associated with cannabis intoxication—such as clouding of mental processes, disorientation, confusion and marked memory impairment—are similar to those produced by other exogenous toxins (64, 112). The syndrome is most likely to occur at high doses and to be dose-related, whereas the panic reactions may occur at any dose unfamiliar to the user (64, 112, 79). The toxic delirium is likely to follow the time course of other drug effects. This syndrome appears to be relatively rare in the United States.

Prolonged reactions

Possible prolonged psychological effects of cannabis use are an area of serious concern and controversy. These include not only psychic reactions but also personality change, change in life style, a possible "amotivational syndrome," "flashbacks" and a possible causal relationship between marihuana use and use of other drugs. Here it is

even more difficult to establish precise cause and effect because the close relationship between ingestion of the drug and acute effects is lacking.

Descriptions of a specific long lasting cannabis psychosis appear largely in the Eastern literature, and thus are largely drawn from a culture where use is generally more frequent, and at higher dose levels, than normally is typical for the United States. This acute "cannabis psychosis" is generally associated with very frequent use and reportedly lasts one to six weeks or longer (64, 112). Recent studies abroad in Jamaica (141), Greece (155) or Costa Rica (23) where frequent users of high potency cannabis were examined failed to document the existence of a specific cannabis psychosis. However, small sample sizes were involved and such a relatively rare occurrence could well have been missed.

A few years ago a clinical report by Kolansky and Moore (95) described eight psychotic reactions in a group of 39 marihuana smokers in this country and attempted to demonstrate a cause-and-effect relationship to their marihuana use. A more recent clinical study demonstrates how correlations between various behaviors and subsequent psychiatric disorders can be misleading (2). Consecutive first admissions to a psychiatric hospital were evaluated. Thirty-eight patients who had used marihuana prior to the onset of psychiatric problems were studied. Indeed, apathy, poor judgment, confusion and depression followed marihuana smoking, but the correlations between marihuana use and subsequent illness was less than with such causally unrelated variables as having masturbated, having experienced sex education, and having drunk beer. In this clinical study marihuana use could not be singled out as a prime factor leading to psychiatric illness.

Marihuana flashbacks—spontaneous recurrences of feelings and perceptions similar to those produced by the drug—continue to be reported (12). The etiology of such flashbacks remains obscure, but those who experienced them seem to require minimal treatment, if any.

Nonpsychotic prolonged adverse reactions

Surveys of user and non-user populations provide some information as to neuropsychological changes, changes in life style and the so-called amotivational syndrome associated by some with cannabis use. In an all too rare prospective study, Culver and King (28) compared groups of LSD-mescaline users with marihuana-hashish users and non-drug using controls. The investigators used a sophisticated psychological test battery including the Halsted-Reitan tests, the Wechsler Adult Intelligence Scale and tests of spatial perceptual abilities. When tested a year later the LSD-mescaline group scored least well on the trail making test but the performance of all three groups fell within normal limits. No evidence could be found for the existence of a neuropsychological deficit with either light or frequent cannabis use. Another study of heavy drug users using a similar test battery arrived at similar conclusions (13). However, the authors of the study remind their readers that one should not conclude that no organic changes occurred since psychological test data is inferential and definitive statements as to organic changes can only be based on radiological or pathological evidence. One study of multiple drug users in the Navy found a large number of psychiatric symptoms reported by them on

the Cornell Medical Index but because of the variety of drugs habitually used it was impossible to single out marihuana use as an important factor (61).

The possible effects of cannabis on student performance has been a major concern because of the extensive use by that group. A longitudinal study of a sample of 1,970 college students examined the relationship between cannabis use and psychosocial adaptation and academic performance (11). Users and non-users did not differ in grade point average or in educational achievement, but the marihuana users seemed to have more difficulty in deciding on career goals and dropped out of college more often to reassess goals. A smaller percentage of regular users planned to seek advanced or professional degrees. There was, in the opinion of the users themselves, a poorer academic adjustment among the most frequent users than among infrequent or non-users. Only 6% of non-users reported a worsening of their emotional state since beginning college but 20% of the long duration users reported negative changes in emotional state. A problem with the study was that a significant percentage of the initial sample was lost over the three year period. If the loss was from the group who failed out or dropped out, those most likely to show loss of motivation or intellectual functions may have been automatically excluded from the study. Also, the study merely reported the students' own assessment of their adaptation since no interviews were attempted. Other questionnaire surveys reported differences between users and non-users but the question of causation remains and the mental health significance of some of the findings are unclear. Non-users scored higher on needs for achievement and order and not surprisingly had higher grades (152). Other surveys found marihuana users to be more dissatisfied, disillusioned and alienated (29), more oriented towards the past (88), but to be more creative and adventuresome (60). They also had lower levels of achievement (16).

The ability of cannabis users to work in other contexts has been examined in attempts to see if a measurable "amotivational syndrome" exists (113, 111). In a study of frequent and infrequent users smoking cannabis while living on a research ward, work output decreased as marihuana consumption increased (111). However, the investigators noted that "motivation" is a function of situational variables as well as drug factors. To term the decrement in work output "amotivational" would imply that the users in the experiment had lost interest in working for money. However, if the work decrement resulted from a drug-induced impairment of performance, it would not be proper to term it a motivation effect. In a similar Canadian study (113) a fall in productivity (making stools) followed the smoking of cannabis. The decreased productivity appeared to be due to less time spent working rather than to decreased efficiency. The authors interpret this as indicative of an "amotivational syndrome." To the extent that these types of studies involve artificial work conditions and tasks dissimilar to more usual employment, it is hazardous to draw more general conclusions regarding the role of cannabis in a more generalized amotivational picture. Moreover, these studies involved intensive daily use. Their relationship to episodic or less frequent use in altering motivation is unknown.

An assumed relationship between cannabis use and the use of other drugs (mainly opiates) has been a source of concern. The progression hypothesis is a good example of a theoretical construct repeated so many times that it has become verified by repetition rather than by facts (161). The patterns of the shifts from one drug to another seem to be changing with more of a "progression" to "polydrugs" other than heroin (57). In a military population the pattern of drug use and selection of drugs was determined more by availability, peer pressure and drug use fads than by pharmacologic or personality variables (123). Cannabis users are, however, very likely to use other licit and illicit drugs with a positive correlation between level of cannabis use and the variety of drugs used (122).

Criminal and aggressive behavior

The often discussed possible link between cannabis use and crime or aggressive behavior was the topic of reviews (56, 92) and experimental studies (26, 107, 142). Both reviews (56, 92) concluded that evidence showing marihuana to cause crime is virtually nonexistent. Young prisoners who varied in their degree of marihuana use were compared using a number of personality measures (e.g., MMPI, CPI) (107). Non-users and occasional users had typical criminal profiles. Regular users of only marihuana were better socialized and adjusted, though more deviant, than collegiate marihuana users. Prisoners who used marihuana plus other drugs were the most deviant.

In addition to concern about marihuana use and criminality, the association between marihuana intoxication and hostile human behavior has been a topic of great interest and discussion. The results of observations and self-reports of hostile, aggressive feelings from research subjects intoxicated acutely or chronically with cannabis suggest the usual effects are to decrease expressed and experienced hostility (80, 109, 142).

CHRONIC EFFECTS

Tolerance

Marked tolerance to the effects of cannabis doses commonly consumed in this country is not usually evident, presumably because of relatively infrequent use and the generally low doses of active material. However, as data accumulate from countries where more frequent use of high doses is common (23, 49, 141, 155), it is apparent that tolerance must develop to many of the psychological and physiological effects. In controlled experimental situations where prolonged administration of THC or marihuana to volunteer subjects has been undertaken, what appears to be dose-related tolerance develops rapidly (8, 53, 80, 109, 111) as judged by behavioral, psychologic and physiologic measures.

In outpatient studies where frequent and infrequent users or other populations with differing drug histories are compared in their response to a given dose of cannabis, the results are less consistent. Marked tolerance to measured effects is rarely obvious, if evident at all (94, 132, 140, 155). However, when sensitive and reliable measures are used, even infrequent use may produce evidence of some degree of tolerance on outpatient laboratory tests (9, 24). Tolerance in man is apparently a dose-related effect as it is in animals (36).

Dependence

When volunteers were given 30 mg doses of THC orally for 10–20 days, sudden cessation of the drug was associated with the appearance of irritability, restlessness, decreased appetite, marked sleep disturbance (including sleep EEG alterations), sweating, salivation, tremor, weight loss, nausea and vomiting, diarrhea and, in general, a clinical picture similar to that following chronic administration and moderate doses of many sedative-hypnotic drugs (8, 48, 80). Such psychologic and physiologic changes have not been commonly observed in other chronic administration studies in this country. Restlessness and weight loss was reported by Mendelson in an inpatient volunteer study at the end of a 21-day smoking period (109). Drug-seeking behavior has not been associated with the withdrawal syndrome, but the presence or absence of such behavior is difficult to assess in the laboratory. A withdrawal syndrome has not been described in recent investigations of chronic users abroad (23, 49, 141).

Field studies of chronic users

Several field studies of populations of frequent long-term users have searched for possible adverse or other effects associated with chronic use (23, 49, 94, 141). These all were concerned with user in countries where high potency cannabis is more readily available than in the United States.

The results of a chronic user study discussed in two previous reports were recently published in book form (141). The 30 experimental subjects had been smoking high potency cannabis almost daily for ten years or more. Few psychological or physiological differences between the cannabis smokers and nonsmokers were evident. There was no evidence for liver, kidney or cardiovascular malfunction. While no differences in chromosomal abnormalities were found, the results must be regarded as inconclusive because of various technical deficiencies of the study. Modest decreases in pulmonary function and altered hemoglobin levels were the only physiologic differences evident. The impact on these findings of tobacco use by the subjects is uncertain. After smoking cannabis, a small group of workers produced less work (weeding, hoeing, digging) with more movements, but otherwise showed no evidence of "amotivation." The importance of cultural differences in the interpretation of drug effects is evident in that people in Jamaica did not find their appetite increased by cannabis, nor their hearing enhanced nor their time sense altered, and in fact said they used cannabis so as to work better. Although reassuring, the findings should also be judged in perspective. They were derived from a small group of selected users, so that rare consequences (if they did occur) such as brain atrophy or psychosis might not have been detected. The subjects were laborers and farmers in a very different culture, so that intellecual impairment may have been relatively difficult to detect.

A similar although larger and more complex study is underway in Costa Rica. Coggins presented a preliminary report (23). Eighty daily marihuana users and matched noncannabis-using controls were evaluated with extensive medical examinations, laboratory studies, X-rays, EEG, EKG and neuropsychological testing. Although the

study is still in progress, no evidence for a greater incidence of disease or deterioration has yet to be found.

In studies of Greek and chronic hashish users approximately 47 chronic users were compared with 40 control nonusers on a variety of EEG, echoencephalographic, neuropsychologic and experimental laboratory tests (49, 94, 155). Conventional clinical measures of brain damage (EEG, echo-EEG) showed no evidence of abnormality in the chronic users. Tolerance to administered doses rapidly developed on the EEG indices. No evidence of withdrawal symptoms after three days of chronic administration was evident. When given high doses of THC, some of these very experienced subjects developed unpleasant psychological symptoms when their tolerance level was exceeded. These were all outpatients so no precise control over drug use outside of the laboratory was possible. A slightly higher incidence of personality disorders in the hashish-using group was better explained by psychosocial variables than by marihuana use.

Thus, these three field studies of users abroad do not report brain damage, psychosis or an "amotivational syndrome." However, the cultures are different, and the sample populations are relatively small so such drug effects can not be ruled out. They may be simply uncommon or difficult to measure.

Chronic effects—laboratory studies

A number of groups have studied the effects of daily cannabis use in paid volunteer subjects consuming cannabis for up to 72-day periods while hospitalized (8, 48, 53, 80, 109, 111, 113). Although even 72 days is not really chronic use, such studies complement the more commonly performed acute outpatient studies. In general, in all these chronic or subchronic studies, subjects have tolerated the drug treatment phase well and very few dropouts, psychoses, or other blatant manifestations of distress were revealed. Except for the pulmonary function changes noted in one study (109), drug effects on mental, behavioral and physiologic functions appear to disappear rapidly on cessation of drug administration and have been, in general, similar to those seen in acute studies. Tolerance is evident at lower doses (53, 109) and obvious at high doses (80).

Adverse physiologic effects associated with chronic use

Mention has already been made of the endocrine and immunologic changes reported in some populations of users. Mutagenesis and teratogenesis is discussed elsewhere in this report. A discussion of the report of brain ventricle changes was presented in a previous report. A paper describing the same group of subjects appeared this past year (46), but no similar reports have yet appeared. The difficulty of performing pneumoencephalograms in neurologically normal volunteers makes survey studies impossible. A number of groups are testing cannabis users with noninvasive techniques for measuring brain ventricle size (computerized tomography) and preliminary results should be available soon. An investigator who reported the electrical changes in the deep brain structures of a human smoking marihuana has now completed chronic studies in monkeys, finding similar electrical changes. The slow wave activity persists for months after the cessation of a chronic period of smoking. The behavioral and biological significance of the changes in man is uncertain.

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CHAPTER 8

Effects of Marihuana on the Genetic and Immune Systems

The effects of marihuana and other cannabis preparations on the genetic and immune systems have recently been areas of intensive research. Since the fourth Marihuana and Health report, a wealth of new information has become available.

ANIMAL STUDIES

In the area of preclinical investigations, chromosome studies in rats and hamsters have been negative (23, 35). However, cytological and cytochemical studies of hamster lung cultures (18) exposed to smoke from marihuana and tobacco cigarettes found an inhibition of DNA synthesis and cell division, abnormalities in mitosis, and variable DNA content in chromosomes. Recently, THC was found to reduce the number of lymphocytes and leukocytes and inhibit the hemolytic plaque forming cell response (a measure of antibody producing cells) in mouse spleens (16). In another study (13), an increase in lymphocytes in rat bone marrow accompanied inhibition of myelopoiesis following administration of delta-9-THC. There is also the report by Harris et. al. (11) that delta-9-THC administered orally to mice retarded tumor growth and increased survival 36%. Harris and associates also observed in another set of experiments that the acute administration of delta-9-THC inhibited 3H-thymidine uptake into the DNA of tumor cells but not into the DNA of bone marrow, spleen, testes, and brain. If the acute administration of delta-9-THC preferentially inhibits DNA synthesis in tumor cells in humans as well, then the potential usefulness of marihuana as an antineoplastic agent will have to be evaluated. Marihuana may also have potential therapeutic use as an immunosuppressant in transplantation surgery if the findings that it depresses cell-mediated immunity in rodents (20, 32) are substantiated in human studies.

Studies of teratogenicity

Early studies of marihuana indicated teratogenic activity in rats, rabbits, mice and hamsters (7, 8, 36, 37). Recently, Fournier et al. (6) have confirmed the findings in rabbits. Mantilla-Plata and Harbison (21) observed that the teratogenicity of delta-9-THC in mice could be modified by pretreatment with phenobarbital and SKF525A. Phenobarbital partially antagonized THC-induced reduction of fetal body weight, while SKF525A either antagonized or potentiated reduction of fetal body weight depending on the gestational age at which it was administered. In addition, SK525A significantly increased the incidence of THC induced fetal resorptions. By contrast, the studies conducted on rats and rabbits by the National Institute of Drug Abuse

(22) did not show deleterious effects of marihuana on either the pregnant mother or the fetus. This is reinforced by the negative finding by Banerjee et al. (1), that delta-9-THC administered to rats produced no malformations among the fetuses, except for a dose related increase in the incidence of spongy spinal cords. Finally, there is the negative report by Legator et al. (17); a battery of tests (including the host-mediated assay, microsomal activation, blood and urine studies, dominant lethal and cytogenetic—micronucleus—examination) failed to detect any effect of delta-9-THC administered orally in the one mouse strain used in all of these studies. Uyeno (44) reported increasing complications associated with delta-9-THC administration to pregnant rats. Results of a later study (45) unfortunately are not interpretable for lack of controls.

The conflicting reports on teratogenic effects may be due to a number of variables including the specific strain used, route and time of administration and dosage. Well designed research projects utilizing animals are needed to determine under what circumstances marihuana acts as a teratogen in animals and how these findings may be applied to humans. To date, aside from occasional case reports, no systematic human studies on the teratogenic effects of marihuana have been carried out.

HUMAN STUDIES

Chromosome analyses

The assessment of genetic effects in man has been exclusively based on cytogenetic analysis; specifically, the examination of human chromosomes. In vitro cytogenetic studies did not show an increase in the frequency of chromosome breaks following the addition of delta-8-THC (33), delta-9-THC (41) and cannabis resin (24) to lymphocyte cultures, but did show dose dependent mitotic inhibition. Cytogenetic analyses of lymphocyte cultures from chronic marihuana smokers have been contradictory. The majority of these studies have been retrospective with comparisons made between marihuana smokers and controls. Seven studies of this type have been published. Negative findings were reported by Martin et al. (24) on a Jamaican population and by Dorrance et al. (5) on light marihuana users. Gilmour et al. (9) also reported that light marihuana users did not show an increased frequency of cells with aberrations but that polydrug users, all of whom used marihuana heavily, did show a significant increase in abnormal cells. However, the use of other drugs makes it impossible to interpret this increase as due specifically to marihuana. Nahas et al. (31) mentioned increased chromosome damage in chronic marihuana smokers but did not provide further information. According to Morishima (27), this increase was not statistically significant.

The three positive studies of marihuana effects on chromosomes should be interpreted with caution. Stenchever et al. (42) reported a significant increase in the number of cells with breaks in marihuana users as compared to controls (3.4% vs. 1.2%). However, as stated in the fourth Marihuana and Health report, "the biological significance of the findings remained unclear because of several methodological and sampling questions raised by the authors themselves" (22). Herha and Obe (12) reported increased exchange-type aberrations (dicentrics and translocations) in chronic cannabis users. Close inspection of

their data shows that five of the nine aberrations they observed occurred in only one of the eleven subjects. Further, chromatid and chromosome breaks, the most commonly reported type of aberrations, were not included in their analysis; when this is done, there is no longer any difference between users and controls. In the third study (14)—the only one to examine chromosomes from direct bone marrow preparations—the authors reported a statistically significant increase in the frequency of breaks. Again, the increase was accounted for by two of the seven heavy cannabis users; the others showed no breaks. In addition, the total number of cells examined was small, 157 cells for all of the seven subjects. (In drug studies, 50–100 cells per subject are customarily considered minimal.) Since information on the number of cells analyzed for each subject was not provided, it cannot be determined whether the number was evenly distributed among all subjects.

Retrospective studies such as those cited above, with their many uncontrolled variables, make definitive interpretations and conclusions difficult, if not impossible. To resolve the controversy, prospective studies are needed.

So far, the results of only two prospective studies (with subjects serving as their own controls) have become available and both have been negative. Nichols et. al. (34) did not detect an increase in the percent of cells with breaks following the oral administration of hashish extract (containing THC, CBN and CBD), marihuana extract (delta-9-THC alone) and synthetic delta-9-THC to 30 subjects following a variety of schedules. The second study (a 94-day study with 72 days of unlimited smoking of marihuana cigarettes containing approximately 2.2% delta-9-THC) found no increase in the break frequency when baseline and post-exposure values were compared (25). However, subjects in both studies were all marihuana users and their baseline values may already have been elevated above those of non-drug using controls. Thus, even these prospective findings are not definitive.

Effects on chromosome complements have also been published. Leuchtenberger et. al. (18, 19), using an in vitro exposure of human lung cells, reported a relative increase in aneuploid cells. Even more strikingly, Morishima (26) reported that in marihuana smokers, a high proportion of cells (30.6%) contained from 5–30 chromosomes instead of the normal 46. In a subsequent study (28), the in vitro addition of delta-9-THC to leukocyte cultures was found to increase the frequency of cells with abnormally low chromosome numbers. The possibility that these types of cells have been overlooked by other investigators as technical artifacts, or that these cells may indeed be technical artifacts, is not settled. Since it markedly reduces the potential for technical artifacts, use of the flow microfluorometry technique to measure DNA content in intact lymphocytes from marihuana smokers and to compare it with DNA content of nonusers may resolve this question.

At this time, there is no conclusive evidence that the consumption of marihuana causes chromosome damage. Indeed, the two prospective studies carried out as part of large biobehavioral investigations on the effects of marihuana did not show increased break frequencies when baseline and post-exposure values were compared. There are no data available, however, on the long-term consequences of marihuana use.

Immune responses

The immune system of man is compartmentalized into two parts: cell-mediated immunity and humoral- or antibody-mediated immunity. Each is dependent upon a major subpopulation of lymphocytes, the T- or thymus dependent cells and the B- or thymus independent cells, respectively. The initial publication was that of Nahas and associates (31) reporting that in vitro cell-mediated immunity, as assessed by mitogenic (phytohemagglutinin) and allogeneic cell stimulation, was significantly depressed in 51 chronic marihuana users compared to 81 controls. Indeed, it was depressed to a level similar to that seen in patients with known T-cell immunity impairment (uremia, cancer and transplant patients).

Investigations attempting to replicate this finding have led to contradictory reports. Gupta et. al. (10) compared by rosette formation the circulating populations of T- and B-cells in 23 healthy chronic marihuana smokers and 23 normal controls. They found that the mean percentage of T-cells forming rosettes was significantly lower in the marihuana smokers while the percentage of B-cell forming rosettes was simliar in both populations. One might conclude, therefore, that smoking impaired T-cell function. Intradermal testing, however, on a limited subsample of marihuana smokers (including those with low or normal percentages of rosette forming T-cells) revealed no correlation with the presence or absence of a positive reaction to one of more antigens tested. Therefore, the results of this study concerning T-cell function are equivocal: When measured by rosette-formation, T-cell function was impaired; when measured by intradermal challenge, it was not. Petersen et al. (38) also reported significantly lower percentages of rosette-forming T-cells in marihuana smokers, while B-cells remained normal. Although the responsiveness to phytohemagglutinin was not significantly different from that of controls, in that same study the cells from smokers did tend to be less responsive suggesting possible impairment of T-cell function. Serum levels of immunoglobulins G, A and M (a measure of B-cell function) were similar in marihuana smokers and non-smokers. Further, the capability of polymorphonuclear leukocytes to phagocytize killed yeast cells was reduced in smokers (phagocytic activity of polymorphonuclear leukocytes is a necessary prerequisite for the transformation of lymphocytes into macrophages which process antigens in the immune system).

The effects of marcomolecular synthesis (i.e., DNA, RNA and protein synthesis) in lymphocyte cultures from normal controls exposed in vitro to many of the natural cannabinoids have been investigated. Cushman and Khurana (3) reported that in vitro incubation of control lymphocytes with delta-9-THC, cannabinol, and cannabidiol for one hour gave a dose-related reduction in rosettes. DeSoize et al. (4) reported that in vitro addition of the natural cannabinoids (delta-9-THC, delta-8-THC, cannabinol, cannabidiol, cannabichromene, and cannabicyclol) to human lymphocyte cultures all affected DNA, RNA and protein synthesis as measured by uptake of 3H-thymidine, 3H-uridine, and 3H-leucine, respectively. These two laboratories also reported positive findings on cell-mediated immunity. Results obtained by Blevins and Regan (2) confirmed inhibition of DNA, RNA and protein synthesis following the in vitro addition of delta-9-THC to

human diploid fibroblast, neuroblastoma cells and mouse neuroblastoma cells in culture. Further analysis detected no effect on either DNA repair synthesis or uptake of radioactivity labelled precursors into the cell, but did demonstrate that the intracellular pool sizes of these precursors were depressed 50%. This last finding could account for the reduced synthesis reported by others.

All of the studies discussed so far point to impairment of cell-mediated immunity in marihuana users. There are others, however, which failed to confirm such impairment. Silverstein and Lessin (40) in an vivo study evaluated the immunocompetence of 22 chronic marihuana smokers compared to 60 controls by the gross criterion of ability to be sensitized to DNCB (2,4-dinitrochlorobenzene) and found no differences. White et al. (43) using both PHA and pokeweed mitogens in a vitro study, also reported no impairment of mitogen-induced blastogenic response in twelve chronic marihuana users as compared to twelve matched controls. Lau et al. (15) in a prospective study could detect no differences in either peak level of response to PHA or concentration of PHA at which the maximal blastogenic response occurred. However, they did find that in cultures without PHA, the level of 3H-thymidine incorporation was higher in marihuana smokers than controls. These investigators carried out assessments before and after fourteen days of oral doses of 210 mg/day delta-9-THC and at a one-week follow-up. Rachelefsky et al. (39) in a prospective study evaluated the immune system of twelve chronic marihuana smokers before and after 64 consecutive days of smoking unlimited quantities of marihuana cigarettes containing approximately 2.2% delta-9-THC. They found that baseline total T-cells and B-cells were significantly lower than controls but increased to normal by the 63rd day, suggesting that factors other than marihuana smoking may have caused the depression seen at baseline. Response to PHA and allogeneic cells was normal and did not change over time; serum levels of immunoglobulins G, A and M were also within normal limits in their study.

Some progress toward reconciling these contradictory findings will be possible when the impact of certain subtle procedural variations becomes known. For example, Nahas et al. (30), found that the cytotoxic effect of delta-9-THC added to 72-hour lymphocyte cultures for the initial 24 hours could be reversed by prolonged washing of the cells with the nutrient medium RPMI. That is, the level of incorporation of tritiated thymidine at 72 hours was the same in treated and non-treated cultures. They surmised that the negative findings by White et al. (43) may have been the result of the washing procedure used in the isolation of lymphocytes; the cell-bound THC may have been washed away. Nahas et al. also found that THC induced inhibition of thymidine incorporation increased as the serum concentration of the culture medium decreased. This, they suggested, could help resolve an apparent inconsistency between two earlier findings: the Nahas et al. results summarized above (31), which showed marked inhibition of DNA synthesis in a medium with a serum concentration of 10%, and a later study (29) which examined the effect of THC on healthy blood in vitro and found the inhibition to be considerably less with a serum concentration of 20%. However, even this may not be an adequate explanation since in the first study fetal calf serum was used and in the second, pooled human serum.

There is general agreement among investigators that marihuana smokers taken off the street and tested have a reduced number of T-cells as measured by rosette formation. In light of the report by Rachelefsky et al. (39) that the initially low level of T-cells returned to normal while subjects were confined on a ward smoking quality controlled marihuana cigarettes, it may be concluded that some as yet unidentified variable, and not marihuana, may be the cause of the reduced number of T-cells seen in chronic drug users. The relationship between reduced T-cell rosette formation and immunologic function, as assessed by mitogen and/or allogeneic cell stimulation, is not clear since Petersen et al. (38) reported a significantly lower mean percentage of T-cells in marihuana smokers than controls, but no statistically significant differences in PHA responsiveness. There is as yet no evidence that marihuana smokers are more susceptible to diseases known to be associated with lower percentages of T-cells (e.g., cancer, viral infections) and/or reduced responsivity to mitogens. Also, skin testing of chronic marihuana smokers indicates intact and normal T-cell functions. B-cell function, too, appears to be normal regardless of how assessed.

SUMMARY AND CONCLUSION

The retrospective design and other methodological imperfections of most human studies, whether chromosomal or immune, leave much to be desired and preclude definitive conclusions. For example, information on nutrition, health care, recent radiation exposure and drug use pattern—all of which are variables known to affect both the genetic and immune systems—is generally obtained retrospectively from the participating subjects and is, therefore, of dubious validity. The potential inaccuracy of such information may doom any attempt to identify a deleterious effect of a specific drug, like marihuana, even were the composition of illicitly obtained marihuana known. Many of the other methodological questions now plaguing researchers could be settled by the collaboration of several laboratories, particularly those reporting contradictory findings, in a single prospective double-blind research design with appropriate control groups.

There is no information on the teratogenic effects in humans and it may take several generations to detect them. The reports on teratogenic effects in animals are contradictory and further rigidly designed experimental studies are needed to supplement the few done so far.

Bearing in mind the limitations of the studies discussed in this report, there is at this time no conclusive evidence that the consumption of marihuana causes chromosome damage. The studies which have been most carefully controlled have failed to show such damage, but insufficient research has been conducted to allow any definitive conclusions.

A number of investigators have reported results indicating that marihuana may interfere with cell-mediated immunity, but until the inconsistencies between these findings and the negative results which have also been reported are resolved, and until the implications of particular procedural variations are more clearly understood, the question of whether or not THC impairs cell-mediated immunity in

humans remains a moot one. There is preliminary evidence, however, that in certain rodents delta-9-THC depresses cell-mediated immunity and preferentially inhibits DNA synthesis in tumor cells as compared to cells of normal tissue. It is important, therefore, to verify the anti-immune and anti-tumor activity of delta-9-THC in animals since, if these findings are confirmed and found to hold true for humans, delta-9-THC may have potential as an immunosuppressing and antineoplastic agent.

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CHAPTER 9

Therapeutic Aspects

Cannabis is one of the most ancient of healing drugs. It was and is an important folk medicine in many cultures. This fact alone is no reason to expect that it will qualify in today's stringent tests of medical efficacy and pharmacologic toxicity. One should not, however, summarily dismiss the possibility of therapeutic usefulness simply because the plant is the subject of current sociopolitical controversy. The controversy makes its impartial evaluation more difficult, but just because a substance has a potential for harm does not mean that it may not also have potential benefits. Furthermore, unaltered marihuana will not be the ideal preparation if some significant area of usefulness is found. Even its active cannabinoids can be improved upon by synthetic chemists. The benzopyran structure is a unique one which can be modified at many positions on the molecule. If the psychological changes of cannabis are not desired, they can be eliminated. If water solubility is preferred, it can be achieved. Although a good deal of further testing will be needed, there is a promise that certain of the pharmacologic effects of cannabis can be helpful.

When one surveys the specific therapeutic indications, some seem more promising than others. It is possible that cannabinoids may have a contribution to make in the treatment of glaucoma and asthma. Despite the recent finding that in certain animals, delta-9-THC is a convulsant in addition to being an anticonvulsant, some of the synthetic compounds may, one day, be helpful in managing certain forms of epilepsy. Inasmuch as only a single preclinical study (24) has examined the usefulness of cannabinoids in the treatment of tumors, it is much too early to say whether cannabis might have an anti-tumor action in man.

Some role may be found for a cannabinoid as a tranquilizer or a sedative-hypnotic. However, it will have to compete with a number of quite effective drugs already marketed for this purpose. Because of recent contradictory findings, a definite statement concerning the value of cannabis as an analgesic or antidepressant cannot be made at this time, but its antiemetic and euphoriant activity could provide needed relief for cancer patients undergoing chemotherapy. There is no evidence at present that the usefulness of cannabis exceeds that of currently available preanesthetic agents or those now in use for detoxification of patients in various drug and alcohol dependency states.

In addition to the possibility that specific benefits may some day, accrue, another reason for therapeutic interest in the cannabinoids is the possibility that their mechanisms of action may be different from the standard preparations. The elucidation of these mechanisms would be even more important than the finding of another therapeutic agent.

THE ANCIENT LORE

The therapeutic use of cannabis predates recorded history. The earliest written reference is to be found in the fifteenth century B.C., Chinese Pharmacopeia, the Rh-Ya (16). From the Chinese plateau its use as a folk medicine, ritual potion, fabric and intoxicating agent spread to India, the Middle East and far beyond.

An examination of the diverse claims made for cannabis as a medicament during past epochs reveals that many cannot be justified by the current knowledge of its pharmacologic activity. For instance, it had wide use as a lotion and poultice for a variety of skin afflictions. It had purported effectiveness in cases of leprosy, gonorrhea and arsenic poisoning. The smoke was tried in enema form for strangulated hernia and an application of the juice of the leaves was recommended for dandruff and vermin infestation.

On the other hand, a rationale can be found for certain of the early medicinal practices. Cannabis was widely used in painful conditions like neuralgia, dysmenorrhea and toothache and its relaxant and euphoriant properties may well have been utilized in the treatment of melancholia and hysteria. Because of its purported analgesic effect, supported by some recent findings, cannabis also found service in minor operations like circumcision and boil lancing.

Cannabis was one of the most important drugs in the Indian Materia Medica at the turn of this century (54). It was, and is, widely used in rural areas of the Indian subcontinent for asthma and bronchitis. A bronchodilator action has recently been quite well established, but cannabis is more likely to be a cause of, rather than a cure for, bronchitis. It was known to be an appetite stimulator; and this usage is confirmed in numerous subjective reports, although no precise mechanism for assessing the appetite-enhancing effect is available.

One interesting effect of bhang and ganja as reported by the Indian Hemp Drug Commission, and more recently from Jamaican (57) and Costa Rican studies is the assertion that it is a "creator of energy"—that it increases staying power, relieves fatigue and is a stimulant. The Jamaican report told of its use as an energizer and motivator to work. Ganja breaks in back country Jamaica seem to be the equivalent of the North American coffee breaks. Employers have been known to supply their workers with ganja to "get more work out of them." This reason for use among laborers and farmers stands in sharp contrast with our concerns about a marihuana-induced "amotivational syndrome."

The scattered but persisting reports about an aphrodisiac property are not easy to evaluate. Much seems to depend upon the mental set of the consumer. If it is taken for that purpose, sexual interest, activity and enjoyment are likely to be enhanced. On the other hand sexually abstinent Indian monks used cannabis to diminish sexual drives and as an aid to meditation. While it may enhance sensory perception, prolong the subjective experience of time and reduce inhibitions, and thus intensify sexual experience, cannabis appears to have no direct effect upon sexual drive states (7). In fact, in view of the reports of lowered plasma testosterone levels after heavy usage, potency may, in some instances, be reduced (35).

Many therapeutic references can be found regarding the seeds of Cannabis sativa (23). For example, the seventh century Scythians inhaled and bathed in the vapors of hemp seeds thrown onto a fire, and "they howled with joy." The seeds contain essentially no active tetrahydrocannabinols, so that whatever joy there was must have been due to the effects of the sauna. A persistent theme that runs from ancient times up to the present is the healing effect of external applications of cannabis. The potential efficacy of cannabis as a topical antibiotic has been most extensively researched in Czechoslovakia (30).

THE MIDDLE PERIOD

During the latter half of the nineteenth century a resurgent interest in the medical usefulness of the hemp plant developed. Well over a hundred papers appeared in the medical journals of the day. Some of these reports are worth citing, however briefly. In Calcutta, O'Shaugnessey (47) tried cannabis on patients with a variety of ailments, including tetanus, rabies, epilepsy and rheumatism. He reported favorably on its anticonvulsant, analgesic and muscle-relaxing properties. This sparked a flurry of clinical investigations including those of M'Meens (42) who considered it a sedative-hypnotic, useful in such diverse disorders as neuralgia, dysmenorrhea, asthma and sciatica. Many favorable reports appeared, including those of Birch (3) and of Mattison (37) who recommended cannabis enthusiastically for the treatment of morphine, alcohol and other addictions. In 1890 Reynolds (55) wrote of its value in senile insomnia and tic douloureux (trigeminal neuralgia).

During this period Moreau de Tours (43) successfully treated obsessive compulsives, melancholics and patients with many other chronic psychiatric syndromes. His positive findings were confirmed by some, but not by other studies.

Despite the encouraging testimonials about cannabis, the drug began to fall into disuse at the beginning of the twentieth century. In retrospect, it would appear that the following reasons combined to account for its neglect:

(1) Different batches of the plant had widely varying potencies, with some essentially ineffective and others stronger than the prescriber expected;

(2) The drug had a poor shelf life. Many of the extracts of cannabis were practically inert by the time they were dispensed. Delta-9-tetrahydrocannabinol gradually breaks down into cannabinol at room temperature or when exposed to daylight and air. *Cannabis sativa* was, therefore, unreliable, and some of the contradictory clinical opinions might be explained on this basis.

(3) Delta-9-THC is extremely insoluble in water and crosses the gastrointestinal wall with difficulty. It is for this reason that the oral route is two or three times less effective by weight than the pulmonary.

(4) Synthetic, water soluble analgesics and hypnotics which had a much more predictable, stable pharmacological action were beginning to appear.

(5) The final blow was the Marihuana Tax Act of 1937 which classified the drug as a narcotic. By that year, however, it was hardly employed in medical practice in the United States.

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Even when the first synthetic tetrahydrocannabinol, pyrahexyl (Synhexyl), became available for clinical trials, it was not widely employed. Some work was done by Thompson and Parker (67), who treated various drug withdrawal syndromes with some success. In what may have been the first double blind study with a cannabinoid, Parker and Wrigley (48) administered it to 57 depressed patients. They were unable to demonstrate a significant difference between pyrahexyl and the placebo. This study has been criticized by Grinspoon (23) for having used an inadequate dosage level. At any rate, both favorable and unfavorable reports with pyrahexyl can be found in the literature. It was tried in depressions, epilepsy and in addictive states. The value of many of the earlier reports is indeterminate. They were uncontrolled, poorly designed and impressionistic. Still, they did provide certain clues which have been exploited in present day pharmacologic investigations.

THE CURRENT PERIOD

The systematic study of the clinical pharmacology of cannabis is less than ten years old. It required a number of scientific advances and administrative decisions before it could begin. These included:

(1) The total synthesis of delta-9-THC by Mechoulam (38) permitting the manufacture of sufficient material for investigators.

(2) The clarification of the relationship between delta-9-THC and the plant material (39).

(3) The development of a source of uniform, assayed marihuana by the University of Mississippi group (52) under a NIDA contract.

(4) The availability of a reliable assay procedure for delta-9-THC in marihuana.

(5) The funding of animal and human studies designed to clarify the physiologic, pharmacologic and psychologic effects of cannabis.

(6) The availability of various cannabinoids for research purposes from the National Institute on Drug Abuse.

(7) The recent development of assay methods which can qualitatively identify cannabinoids in biological fluids (1).

Cannabis has been found to have some therapeutic potential in a number of diverse areas. They can be divided into two general groups, those that utilize the psychologic changes that the drug induces and those that do not. In the latter instance, the subjective symptoms often become undesired side effects of the drug.

The non-psychologic research directions includes intraocular pressure reduction, bronchodilator, anticonvulsant and tumor growth retardation.

The therapeutic efforts which rely on changes in the psychic state are: sedative-hypnotic, analgesic, antidepressant and tranquilizer, preanesthetic, antinauseant and antiemetic, and drug and alcohol dependence therapy.

Intraocular pressure (IOP) reduction

Hepler and associates (25, 26) undertook a study of the various ocular alterations produced by smoking cannabis in 1970. Among their early findings were a consistent, dose-related, clinically significant fall in IOP in subjects with normal ocular tension. The IOP was also re-

duced with oral delta-9-THC and, to a lesser degree, with cannabinol and cannabidiol. Seven of eleven patients with ocular hypertension demonstrated a drop in IOP averaging 30% which lasted four to five hours. Topically instilled delta-9-THC in sesame oil produced a 40% reduction in IOP when compared to a treatment of sesame oil eye drops administered to a group of twelve rabbits.

Green et al. (20, 21) demonstrated a fall in the IOP of rabbits given intravenous delta-9-THC. They postulated that delta-9-THC interacted with the adrenergic innervation system of the eye, namely that alpha-adrenergic blocking agents partly inhibited the THC effect. Apparently, beta-adrenergic blockade also dampens the delta-9-THC effect. The result of these adrenergic activities is a dilation of the efferent blood vessels. These effects were found to be modulated via an inhibition of prostaglandin synthetase.

Cooler and Gregg (12) compared intravenous (i.v.) doses of 1.5 and 3 mg of delta-9-THC, 10 mg diazepam (Valium) and a placebo in ten volunteers. IOP was diminished 29% with the low and 37% with the high delta-9-THC dosages. Diazepam lowered the pressures 10% and placebo 2%. These investigators also measured analgesia and noted no cutaneous or periosteal analgesic effects. Their subjects manifested an increased anxiety level on both doses of delta-9-THC. This study and others indicate that the IOP reduction is not due to any relaxing or euphoriant effects of cannabis as suggested by Flom et al. (18).

Bronchodilation

During 1973 two articles referring to a bronchodilator effect appeared. Vachon et al. (68) studied the effects of a single administration of smoked marihuana on normal subjects and asthmatic patients. Airway resistance decreased significantly permitting an increase in specific airway conductance and mean expiratory flow rates. The bronchoconstriction of the asthmatic patients was reversed for hours.

Tashkin et al. (64) did a double blind study of 32 non-naive, male subjects randomly assigned to a placebo group, a 1% delta-9-THC and a 2% delta-9-THC group. The investigators found that both dosages decreased airway resistance with a peak at fifteen minutes and with activity still present after an hour. Subsequently, they examined dose response curves with a placebo and 10, 15 and 20 mg of oral delta-9-THC and found that peak effects for the THC dosages were obtained at three hours. Persistent effects were evident for six hours.

Tashkin and associates also induced bronchospasm in asthmatics with methacholine or exercise (65). In a single blind fashion 10 mg of smoked delta-9-THC was compared to 1.25 mg of inhaled isoproterenol (Isuprel), both placebo controlled. Bronchospasm was relieved promptly by both drugs, not by their placebos. The isoproterenol had a higher peak effect, but the marihuana had a longer lasting activity.

The irritant quality of smoked cannabis, with its terpenes and coal tars, makes it poor delivery vehicle for asthmatics. At present, an aerosolized delta-9-THC is being tried (46). The results of a pilot study are encouraging, showing that the aerosol produced a mean peak increase above baseline of 89%—much greater than the increase observed when the same amount (10 mg) of delta-9-THC was smoked. Also,

systemic effects such as the tachycardia and the "high" were not as pronounced with the aerosolized preparation.

This group also attempted to clarify the mechanism of bronchodilator action (59). In one set of experiments, six young males either smoked a cigarette containing 10 mg delta-9-THC or were injected with atropine before being challenged with methacholine. In contrast to atropine the cannabis-induced increase in specific airway conductance was not blocked by a methacholine challenge. In succeeding sets of experiments, the effects of combinations of propanolol and marihuana and isoproterenol and marihuana on young males were examined. Unlike isoproterenol, propanolol did not block the cannabis-induced increase in specific airway conductance. Apparently, cannabis is a bronchodilator independent of beta-adrenergic or antimuscarinic effects.

Anticonvulsant

Much of the work investigating the anticonvulsant properties of cannabis has been preclinical. The effects of cannabinoids on animal seizures resembling epileptic attacks, whether induced by pentylentetrazol (Metrazol)or by audiogenic or electrical means, have been recently examined. Consroe et. al. (8, 9, 10) found that delta-8- and delta-9-THC blocked all three types of seizures in a dose-related manner, and that these cannabinoids were qualitively comparable to diphenylhydantoin (Dilantin). Boggan (4) confirmed the effect of delta-9-THC in audiogenic seizure susceptible mice.

Rat hippocampal seizures precipitated by afferent electrical stimulation were used in another study of anticonvulsant activity (17). Cannabinoids were effective—more effective than diphenylhydantoin—in diminishing these seizure discharges. Cannabidiol was most potent, followed by cannabinol, delta-9-THC and delta-8-THC in order of effectiveness. Interestingly, the psychologically non-active cannabinoids outperformed the active ones.

Karler et al. (31, 32, 33) showed that tolerance developed to the anti-seizure activity in the maximal electroshock test in rats treated with delta-9-THC and in mice treated with delta-9-THC, cannabidiol, diphenylhydantoin and phenobarbital. In other electrical seizure models tolerance was variable and specific for each model. It is possible that cannabidiol, which has no psychotoxicity or cardiotoxicy, has the further advantage of being a better anticonvulsant than delta-8-THC. Mechoulam (40) reported that 6-oxo-cannabidiol diacetate is a promising anticonvulsant.

The Davis and Ramsey pilot study in 1949 (13) examined the effect of tetrahydrocannabinols on five epileptic hospitalized children who had been receiving diphenylhydantoin or mephenytoin (Mesantoin) as medication. Two cases showed improvement after receiving one cannabinoid, while transfer to a second cannabinoid produced mixed results. Very little human investigation of the anti-epileptic properties of the cannabinoids has been done since.

Convulsant as well as anticonvulsant action has been demonstrated for cannabis. This is usually manifest when toxic or high chronic doses are used. However, Consroe et al. (11) have bred a strain of New Zealand rabbit which is quite susceptible to delta-9-THC seizures. Doses of 0.1–0.8 mg/kg i.v. produced behavioral seizures regularly.

Spontaneously epileptic beagles were given delta-9-THC, cannabidiol or a placebo for twenty consecutive days. Myoclonic jerks and generalized seizures were observed only in those dogs receiving 3–5 mg/kg orally. A single case report suggests that cannabidiol may activate spiking in epileptic patients (69).

In view of the problems involved with delta-9-THC (insolubility, variable oral absorption, psychotoxicity, tachycardia, convulsant potential), three new benzopyrans have been synthesized (51). These are dimethylheptylpyran (DMHP) analogues which are more active than diphenylhydantoin in rats given the supramaximal electroshock test. These new compounds have varied anticonvulsant profiles, do not produce tolerance and have minimal toxicity.

Retardation of tumor growth

Harris et al. (24) have reported that mice inoculated with Lewis lung adenocarcinoma materials showed reductions of tumor size from 25 to 82%, depending upon the dose and duration of treatment, with subsequent administrations of oral delta-9-THC, delta-8-THC and cannabinol, but these investigators did not find such an effect with cannabidiol. Cannabinoids increased survival time by a quarter to a third compared to an increase of about 50% for cyclophosphamide. Friend leukemia virus growth was also inhibited by delta-9-THC, but L1210 murine leukemia was not. In vitro experiments confirmed the animal inhibition of growth, leading the authors to conclude that certain cannabinoids possess antineoplastic properties by virtue of their interference with RNA and DNA synthesis.

The therapeutic studies which rely upon the psychologic effects of marihuana follow.

Sedative hypnotic

Freemon et al. (19) confirmed the observation of others that delta-9-THC, like most hypnotics, reduces REM time during sleep. However, in contrast to findings with other hypnotics like the barbiturates, the abrupt withdrawal of THC after six consecutive nights of usage failed to produce a REM rebound, although mild insomnia was observed. Sofia and others (61) have demonstrated that pretreatment of laboratory animals with delta-9-THC reduces the dose of barbiturates needed for hypnosis and increases sleep time.

Studies attempting to exploit the well-known relaxing, sedating properties of cannabis have been performed. Two studies conducted by Neu and his colleagues (44) exploring the use of delta-9-THC as a bedtime sedative are difficult to reconcile with one another. In the first study nine subjects with sleep difficulties were given 10, 20 or 30 mg of delta-9-THC or a placebo at weekly intervals, double blind. The drug, as compared to the placebo, significantly reduced the time needed to reach a state of sleep. Furthermore, sleep was less interrupted during the drug nights. Side effects were mild, but they grew in number with increasing dosage. The main complaint was of feeling hungover or "stoned" the next day.

In the second study the delta-9-THC doses were reduced to 5, 10 and 15 mg to reduce hangover. These were compared to a placebo and to 500 mg of chloral hydrate, a well-established hypnotic. Surprisingly, neither the chloral nor the delta-9-THC facilitated sleep induction or

extended the duration of sleep as compared to the placebo. At the 15 mg dose level, some complaints of hangover were recorded. The authors suggested that difficulties in controlling the room temperature during the winter may have interfered with sleep sufficiently to negate any possible hypnotic effects of the active substances.

Tassinari et al. (66) reported increases in total sleep time in eight volunteers. Stage II sleep was increased and REM sleep was reduced. The doses used were rather large (0.7 to 1 mg/kg of delta-9-THC).

Analgesic and pre-anesthetic

One of the earliest folk uses for cannabis was its pain-relieving quality. A series of preclinical investigations by Kaymakalan et al. (34) tended to confirm the analgesic effect. After having received intravenous administration of 1 mg/kg delta-9-THC, dogs received electric stimulation through an implanted dental electrode. The cannabinoid produced a definite analgesic effect, as shown by a fourfold increase in pain thresholds. Tolerance to analgesia, sedation and ataxia occurred in eight days. In another study delta-9-THC produced pain reduction in mice and rats as measured by the tail flict and writhing tests, and in rabbits receiving sciatic nerve stimulation. The analgesia produced with the doses used was equivalent to morphine analgesia—in fact, in rats a cross tolerance between delta-9-THC and morphine was found. An earlier study (49) measured the effect of delta-9-THC on rats with electrodes implanted in aversive brain sites. A non-dose related elevation of the pain threshold and an attenuation of the escape response were recorded.

A double blind Canadian study by Milstein (41) revealed a significant increase in pain tolerance among those who had smoked marihuana. Using a pressure algometer, the experimenter found that experienced subjects obtained greater analgesia than non-experienced subjects, although the increased pain tolerance was found only in the preferred hand. No effects on sensitivity to pain sensation were noted.

In another human study Hill et al. (27) recorded opposite results. Here, 26 subjects received blind either marihuana smoke containing 12 mg of delta-9-THC from a spirometer or a marihuana placebo, then were given electrical skin stimulation. The THC was found to decrease tolerance and heighten sensitivity to pain.

In an impressionistic report Dunn and Davis (15) questioned ten paraplegics hospitalized in a V.A. Hospital, all of whom had admitted using marihuana in the past. Four reported that it produced a decrease in phantom pain sensations, five mentioned a decrease in spasticity, and five noted a decrease in headache pain and an increase in pleasant sensations.

Cancer patients in pain were studied by Noyes et al. (45). Patients were given either delta-9-THC in 5, 10, 15 or 20 mg doses or a placebo. Pain reduction was greater at all delta-9-THC levels than in the placebo condition and significantly so at the 15 and 20 mg THC levels. These researchers felt that the pain relief was not due to the sedative or euphoriant effects.

Antidepressant

Since marihuana tends to elevate mood, it follows that an evaluation of its antidepressant potential would be sought. Kotin et al. (36) administered 0.3 mg/kg of delta-9-THC or a matching placebo twice

daily to eight patients who required hospitalization for their affective disorder. The patients were all considered moderately or severely depressed. Treatment lasted a week, with placebos substituted for the active drug thereafter. No evidence of a significant affectual change could be demonstrated. In chronic depressive states a longer duration of drug administration is sometimes needed.

A group at the Medical College of Virginia (53) performed a double blind study with cancer patients receiving chemotherapy. An initial starting dose of 0.1 mg/kg t.i.d. was used which was raised if previous doses were well tolerated. On a battery of personality tests and mood scales the delta-9-THC acted as a mood elevator and tranquilizer producing significant improvement on two or three Zung depression scales. Cognitive functioning was unimpaired and appetite enhancement and retardation of weight loss were noted from the clinical records. The need for narcotics was decreased, and patients had the impression that some pain relief resulted. Relief of nausea and vomiting was problematic.

Pre-anesthetic

A number of studies have examined the role that delta-9-THC can play as a preanesthetic agent, with mixed results. When it was given prior to inhalation anesthesia, the requirement for cyclopropane and halothane was decreased (50, 62). Smith (60) found that normal volunteers given 200 mcg/ THC intravenously experienced marked sedation with minimal respiratory depression. Also, salivation was diminished, bronchodilation occurred, and cardiac output increased on the basis of the expected tachycardia. Although the author cautioned that some of the observed effects may have been due to the alcohol in which the delta-9-THC was dissolved, that amount of the drug given intravenously could easily have provided the manifestations recorded. Whether delta-9-THC has a potential usefulness in anesthesiology will depend on findings from additional studies.

Gregg and Small (22) found two dosage levels of intravenous delta-9-THC ineffective in controlling anxiety in oral surgery patients. In fact, in low doses it elevated anxiety, sometimes to a marked degree. Intravenous diazepam (Valium) outperformed the drug under investigation.

Smith (60), having searched for suitable pre-anesthetic combinations, reported that 5 mg of delta-9-THC intravenously produced fear in a number of patients. In combination with an opioid it provided useful sedation but with a marked decrease in carbon dioxide sensitivity. When combined with a barbiturate, the CNS depression was unpleasant and associated with some restlessness, but the response to carbon dioxide was unchanged. With diazepam definite drowsiness and other depressive effects were notable, and the ventilatory response to carbon dioxide was decreased. The investigator suggested that the combination of marihuana with pre-anesthetic or anesthetic medications could lead to undesirable potentiation.

Johnstone et. al. (29) also examined delta-9-THC in combination with other drugs. THC was administered intravenously after subjects had been pretreated with oxymorphone (OXM) or pentobarbital (PBL). The sedative effects of OXM were increased by THC, but the cannabinoid also increased respiratory depression. The combination

of PBL and THC did not cause respiratory depression but produced such intense anxiety and psychotomimetic reactions that four of the seven subjects receiving this combination were not given the full course of five THC doses. The investigators concluded that neither combination was a desirable anesthetic premedication and also expressed reservations about the value of THC alone for such a purpose.

Antinauseant and antiemetic

Sallan (58) gave two oral courses of delta-9-THC or a placebo to a small number of cancer patients in chemotherapy who were not responding well to the conventional antiemetics. Nausea and vomiting were brought under control with the drug significantly more often than with the placebo. Sedation, which could be considered desirable in this group of patients, was a frequent side effect.

Alcoholism and drug abuse

Rosenberg (56) has studied the response of a group of alcoholics and normal volunteers to marihuana cigarettes (0.4 gm/50lb body weight) and to alcohol (2 ml vodka/kg). This investigator found that alcoholics tended to be less responsive to stress (mental arithmetic and talking to a videocamera) and were more likely to withdraw from a stress situation than the normals. Alcoholics became more angry and depressed after alcohol ingestion as measured by mood scales. Marihuana produced a more positive mood state and did not interfere with the arousal reaction, although it greatly increased heart rate and produced an acute paranoid or confusional state in 3 of the 27 subjects. This investigator also found that disulfiram (Antabuse) and marihuana could be given safely together in the treatment of alcoholism. The study is continuing, but the early findings indicate that marihuana may be a suitable therapeutic adjunct for some alcoholics.

Hine and colleagues (28) have implanted morphine pellets in rats. Delta-9-THC in 1, 2, 5 and 10 mg/kg doses was injected 71 hours later. After one additional hour, 4 mg/kg of naloxone (Narcan) was delivered. The two higher doses blocked the appearance of wet shakes, escapes, diarrhea and increased defecations, although neither delta-9-THC nor cannabidiol precipitated abstinence in these rats. The results indicate that delta-9-THC may be worth studying in narcotic detoxification situations.

Mechanism of action

The precise mechanism by which cannabis exerts its various pharmacologic effects is not known. Burstein (5, 6) found that delta-9-THC reduced prostaglandin formation by inhibiting prostaglandin synthetase. Other cannabinoids also have this effect, as does olivetol, from which delta-9-THC is synthesized. Many prostaglandins exist, and it will be necessary to determine what effect the cannabinoids have on the various fractions. Prostaglandin inhibition would explain a number of the physiologic actions attributed to cannabis such as the intraocular pressure reducing and bronchodilating effects.

The influence of cannabinoids on neurotransmitters has been examined, but the results are inconsistent. Banerjee et al. (2) have shown that the psychologically active cannabinoids and cannabidiol are potent inhibitors of norepinephrine, dopamine, serotonin and GABA in

vitro, while the cannabinoid-biogenic amines relationship is undoubtedly much more complex. Drew and Miller (14) believe that cholinergic dominance best explains the mental effects. Monoamine oxidase inhibition of the various cannabinoids is also beginning to be studied.

SUMMARY

The further study of the cannabinoids for various therapeutic applications seems worthwhile. Numerous synthetic cannabinoids have begun to appear; these do not have the disadvantages (insolubility, undesired psychic effects, instability) intrinsic in the naturally-occurring ones. Therapeutic efficacy may also be enhanced by molecular manipulations. Thus, it is likely that if any cannabinoid achieves clinical acceptance, it will be a synthetic.

Findings of importance are: 1) the wide safety margin between effective and lethal doses, of cannabinoids; and 2) that in many instances the mechanism of action appears to differ from the medication commonly employed. The hemp plant and its derivative chemicals turn out to be neither the best nor the worst of substances. Like everything else it should be used for its beneficial effects and avoided for its noxious aspects.

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